



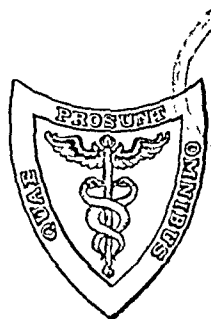
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ORIGINAL ARTICLES.

STRESSES AND STRAINS OF HOMEOSTASIS.\*

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THE extraordinarily unstable stuff of which our bodies are constituted is persistently subjected to various external and internal conditions which, if not resisted, would profoundly alter its ability to function. Environmental temperatures extending from arctic cold to torrid heat, atmospheres ranging from the tenuous air of high mountain tops to the heavy and perilous murk of deep mines, sudden outputs of acid by the muscles as a consequence of strenuous labor, the losses of water and food reserves in thirst and starvation—all these contingencies occur to human beings in the natural course of experience, and though these hazards might well be expected to be damaging or fatal, ordinarily they are not; indeed, they may not prove to be even dangerous.

How does it happen that we can be so remarkably safe from these accidents of existence? The answer to that question is found in an admirable feature of the organization of our bodies—the arrangement whereby all our living parts, both the gross and the minute, are intimately in contact with fluid, as if immersed in it—the rapidly flowing blood and the more slowly moving lymph. Everywhere inside the lifeless layer of skin which covers us, the organs and tissues are set in a *fluid matrix*. If we make a small opening in the skin, at once the fluid begins to exude or flow away. This “internal environment,” as Claude Bernard called it, has developed as organ-

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isms have developed; and with it there have been evolved remarkable physiologic devices which operate to keep it constant. Though the world outside us may be distressingly cold, though the heat and acid which arise from our own strenuous exertions may tend to become an overwhelming menace, we are not greatly disturbed, for our living parts touch only the body fluids which are maintained in an even and steady state. So long as this personal, individual sack of salty water, in which each one of us lives and moves and has his being, is protected from change, we are freed from serious peril. Because that protection is afforded by special physiologic agencies, I have suggested that the stable state of the fluid matrix be given the name *homeostasis*.

We shall gain insight into the ways in which homeostasis is maintained if we consider for a few moments two general relations of the nervous system. In one relation, through its receptors (or sense organs) and through its control of skeletal muscles which move the bony levers of the body, the spinal cord and brain are concerned with the external environment. Thus we learn, and thus we move from place to place and strive to alter the world about us as we wish. In the other relation, through connections with internal organs—with the heart, the bloodvessels, the gastro-intestinal canal, the liver and other viscera—*via* the autonomic nervous system, the spinal cord and brain are concerned especially with the internal environment. The autonomic system, as is well known, has three parts, the cranial, the sacral, and the thoraco-lumbar or sympathetic divisions. The sympathetic division discharges nerve impulses which accelerate the heart and contract or relax bloodvessels; which dilate bronchioles, set free sugar from stores in the liver, cause erection of hairs; and which stop the special functions of the digestive tract, discharge adrenin from the adrenal glands, and produce still other effects. Since the discharged adrenin is carried everywhere in the body by the blood, and since it has the same effects on the internal organs as the sympathetic impulses, the coöperation of the two agents may be regarded as constituting a sympatho-adrenal mechanism.

It is a point of considerable importance that the sympatho-adrenal system, when strongly excited, appears to act as a unit. No matter what the stimulus, the effect is diffuse and extends throughout the body. The arrangement of nerve connections with sympathetic ganglia favors that sort of effect<sup>1</sup> and the indiscriminate distribution of adrenin by the blood stream supports it. This tendency of the sympatho-adrenal system to act as a whole explains the occasional appearance of inappropriate features in the total complex of the reaction, *e. g.*, "gooseflesh" or the erection of hairs in fever and the increase of blood sugar during asphyxial states. In other circumstances these are useful features of the reaction, as when the hairs are erected in cold surroundings and sugar is dis-

charged from the liver if the glycemic level falls. The significance of this integrated response to a variety of stimuli will become evident later.

For the present I wish to try to make clear that it is the peculiar function of the sympatho-adrenal mechanism to preserve and assure a homeostatic condition in the internal environment. In doing so I shall offer a few illustrations.

When a normal warm-blooded animal is exposed to a cold atmosphere heat begins to be lost from the body to the cooler surroundings, and therefore the temperature of the internal environment might fall. If the animal is provided with hairs or feathers, however, they are erected in such manner as to enmesh a protective layer of poorly conducting air about the body and thus hinder the passage of heat outward. Also the surface bloodvessels are contracted, with the result that the warm blood from the interior of the body is less exposed to cooling. And furthermore, adrenin is secreted, and that acts to speed up the burning processes in the organism and thereby to produce more heat. Thus heat conservation and extra heat production are favored, which serve to keep the temperature even. Because of these arrangements for stable bodily temperature, warm-blooded animals are liberated from the limitations imposed during the winter season on cold-blooded animals, which are condemned to hibernate in sluggish inactivity. The erection of hairs, the contraction of surface vessels, and the secretion of adrenin are all consequences of action of the sympatho-adrenal apparatus. If the sympathetic division of the autonomic system is removed surgically, the animals thus operated upon become obviously defective when exposed to cold. There is no adaptive check on heat loss from the body because hairs cannot be erected, nor can surface vessels be constricted. Also heat production cannot be accelerated by adrenin because the nerves evoking that remarkable hormone are absent. The behavior of sympathectomized animals in cold weather is in accord with this lack of physiologic efficiency. During the winter they live almost continuously in the neighborhood of sources of heat. If placed in a cold room, so cold that water nearly freezes, we have found<sup>2</sup> that they undergo a rapid drop of bodily temperature—sometimes as much as 4° or 5° F.—which occurs although there may be vigorous shivering. Indeed, shivering—which is, of course, muscular activity accompanied (like all such activity) by heat production—is the only resource except exercise that is left to prevent sympathectomized animals from suffering a serious fall of body temperature. Note that the feature which is lacking in such endangered animals is the service of the sympatho-adrenal mechanism.

Another external condition to which organisms may be subjected is that of a lessened oxygen supply. Mountain climbers, and aviators who fly at great altitude, have to make adjustments to that circumstance, because the higher they go, the lower is the oxygen

pressure and therefore the smaller is the oxygen load which the red blood corpuscles carry away from the lungs to the remote cells of the organism. The problem is that of getting enough oxygen to burn the non-volatile acid which is constantly being produced by these cells. Should the blood, which is mildly alkaline, become acid, even to a slight degree, coma supervenes, and often death. If oxygen is adequately supplied, however, the non-volatile acid is burned to volatile carbonic acid and, since that is readily breathed away, the hazards of a severe acidosis are obviated. Clearly the way of avoidance of those hazards is through an adequate oxygen delivery to the tissues, where non-volatile acid is being made. Adjustments which work toward that end occur in the heart, bloodvessels and spleen. The heart is made to beat more rapidly and the bloodvessels are constricted in certain parts of the body, with the consequence that arterial blood pressure is raised; and under the higher head of arterial pressure the flow of blood is more rapid, *i. e.*, the number of trips made by the corpuscular carriers of oxygen from lungs to active tissues is increased. And, as a matter of special importance, the brain, which is peculiarly sensitive to lack of oxygen, and the heart, which needs oxygen continuously because it must be continuously active, are assured most favorable conditions because their bloodvessels are either not narrowed or are actually enlarged. Simultaneously, by contraction of the spleen, extra corpuscles are forced from storage in that organ out into the general circulation. Thereby, not only are the corpuscles more actively employed as conveyors of oxygen, but more corpuscles are called forth into active employment. Now the faster heart beat and the vascular constriction and the squeezing of the spleen are all results of sympatho-adrenal function. In sympathectomized animals, of course, these adjustments cannot take place. In our laboratory, in fact, Sawyer and Schlossberg<sup>3</sup> have found that whereas normal animals exposed to a low percentage of oxygen in the air (6%, for example) will endure the ordeal for at least an hour with no obvious indications of discomfort other than rapid breathing, sympathectomized animals faint and collapse in unconsciousness within a relatively short time—varying from 14 to 38 minutes. This sympatho-adrenal mechanism is clearly of the utmost value in keeping the fluid matrix from developing a dangerous acid reaction.

Not only does the sympatho-adrenal system protect against such perils as cold and low oxygen pressure, which affect the organism from the external world, it also protects against possible harm which might come from internal changes. A few illustrations will help to make that point clear.

Prolonged muscular activity—as, for example, cross-country running—uses the reserves of sugar in the body, and may actually empty the liver of its stored glycogen. The total amount of sugar in the blood at any time is little more than a teaspoonful, and yet

when great and powerful muscles are engaged in hard labor their requirements and the requirements of the nerve cells must be met from this scanty supply. The dose must be constantly renewed. For if the sugar level in the blood falls to approximately half the usual percentage, convulsions result; and if the reduction is not checked, coma and death follow. These facts were discovered by studying the phenomena which occur when the liver is removed and the organism is thereby deprived of its greatest sugar deposit.<sup>4</sup> They can be illustrated also by giving insulin, which, if present in excess, may gravely reduce the blood-sugar percentage. When, by an injection of insulin, the sugar concentration has been lowered about one-third of the usual percentage, a so-called "hypoglycemic reaction" appears, characterized by pallor, rapid pulse, dilated pupils, profuse sweating, and other effects, indicating that the sympatho-adrenal system is active. This system, as previously stated, is able to liberate sugar into the blood from the hepatic storehouse. And it may set free so much that, if the dose of insulin has not been overwhelming, the danger of convulsion is passed, and then the sympatho-adrenal system subsides into inactivity. The prime value of this arrangement can be readily shown in animals from which the sympathetic chains have been removed or in which the adrenal glands have been rendered inactive. Such animals have no effective means of increasing the blood sugar when it is reduced by insulin, and in consequence are extremely sensitive to the action of that substance. In studies of homeostatic regulation, Sawyer and Schlossberg<sup>5</sup> found that a dose of insulin which produces no noteworthy disturbance in normal animals occasions in sympathetomized animals marked symptoms, commonly attended by a convulsive attack and sometimes by collapse.

In considering the physiologic adaptations made when the oxygen pressure in the air is low, I mentioned incidentally the fact that some organs more than others in the body are affected by lack of oxygen. The brain, for instance, is much more sensitive to that condition than are the muscles; indeed, there are cells in the brain which are fatally injured if they are deprived of oxygen for even a few minutes, whereas smooth muscle can go without it for hours and still survive. The ever-active heart, also, has special need for a continuous oxygen delivery. The preservation of a relatively constant flow of blood to these essential organs is one of the most important homeostatic functions. It is assured by a fairly steady arterial blood pressure. When, because of reduced blood volume, the pressure is lowered to about 70 mm. of mercury, the supply of oxygen becomes insufficient for bodily requirements and then sensitive tissues begin to be injured. If, however, a sharp hemorrhage induces a drop of pressure to such a degree, a protective mechanism is brought into action, which, up to a certain point, is able to compensate for the lost blood by raising arterial pressure. Indeed, a considerable percentage of the

total blood volume may be removed and yet the pressure is soon restored to nearly its normal level. That this immediate effect is due to constriction of the bloodvessels, so that their capacity is made to fit the lessened quantity of their content, and is not due to an inflow of fluid from the tissues, is proved by noting that the blood is not diluted. It has long been known that the sympatho-adrenal apparatus is an important agent in this compensatory process. It is not only concerned with maintaining an effective head of pressure after hemorrhage—by reducing the size of the arteries and veins and speeding up the heart rate—but also it helps the situation further by contracting the spleen, as it does when the external oxygen supply is menaced, and thereby presses extra red corpuscles into service. A quantitative comparison of the ability of normal and sympathectomized animals to meet the test of hemorrhage, which was made by my collaborators, Schlossberg and Sawyer,<sup>6</sup> demonstrates vividly the essential rôle of the sympatho-adrenal mechanism in the critical state induced by a considerable bleeding. If the blood is removed in three or four steps, separated only by enough time to permit recovery of pressure, as much as 45% of the estimated blood volume can be removed before the compensating mechanism fails to be effective. In sympathectomized animals, on the other hand, the compensatory reaction to a single removal of 13 to 15% of the blood volume is in some instances strikingly absent and in other instances uselessly slight. Again we note the value of the sympatho-adrenal agency as a protector of homeostasis, homeostasis as a condition for the functioning of essential organs, the heart and the brain.

In the various examples of homeostatic adjustments which I have cited, certain internal or external conditions have been described which have tended to disturb the steady state of the fluid matrix; and the corrective processes have been indicated which have maintained the fluid matrix on its even course. We have seen that evidence points to the sympatho-adrenal system as the chief agency in resisting alterations of our internal environment, for when that system is not functioning the same stresses—cold, lack of oxygen, low blood sugar, loss of blood—which had no considerable influence on normal animals, became ominous for continued existence. In other words, sympathectomy changed the animals so that a stress which previously had been readily endured, afterward produced a breaking strain. It is clear, however, that by increasing the stress—by applying greater cold, by still further lowering the oxygen in the air, by reducing blood sugar to a greater degree, or by withdrawing more blood—the strain on the organism may become too great, even though the compensatory sympatho-adrenal apparatus is working to its utmost. Then the fluid matrix becomes altered. My colleague, R. G. Hoskins,<sup>7</sup> has suggested that it would be of interest and within the realm of possibility to

express the general "vitality" of an individual in terms of a "homeostatic index"—an expression which would state the measured ability to react, without disturbance of the fluid matrix, to a group of standard stresses which might readily disturb it. The chance of gaining insight into the strength and endurance of stabilizing factors of the organism, and thus into its ability to resist the operation of disturbing forces, makes it worth while to enquire where the limits lie beyond which stresses overwhelm these corrective factors and significantly alter the steady state of the internal environment. I have used the expression "significantly alter," because it is clear that in any case the signal for bringing the corrective factors into play is *some* alteration. Indeed, as Richet<sup>8</sup> long ago remarked, our bodies maintain their stability because they are variable! The point at which the stability is "significantly altered" should be defined. Perhaps, as a tentative definition, we may say that it is where the alteration becomes so great as to cause secondary, irrelevant effects and therefore lessens the efficiency of the organism. With that definition in mind, let us consider stresses which may place upon the protective agencies an excessive strain.

Before turning to conditions in the fully grown individual, it is well to recognize that the mechanisms which maintain uniformity in his fluid matrix are, in some respects, certainly not well developed in the newborn. There has been no need for them. The fetus is surrounded by a fluid external environment which does not differ greatly from the fluid internal environment. When born the baby is delivered precipitately from his liquid surroundings into surroundings which are utterly fresh and foreign. The new environment is gaseous instead of liquid; it is cold, it is noisy and brilliant and rough; a gasp fills the lungs with a thin, dry air and then water begins to be lost from the body with every breath. As Stanley Hall remarked, "At birth the child is cast like a shipwrecked mariner by angry waves on a strange and unknown coast and finds himself in a new and rigorous climate." Profound readjustments must be made, and they take time. With respect to temperature control, for example, the human infant is much less stably organized than is the adult. Not only do infants have a larger relative surface through which to lose heat to the outer world, but they are less quick and less effective in the reactions which preserve the normal state when the surrounding temperature varies. In consequence there may be sharp drops in the body temperature on exposure to moderate cold. In one case careful observations revealed that the rectal temperature during the early hours after birth varied from 95.4° to 98.6° F., the lowest point being reached after a bath in water at 102° when the room was at 71°.<sup>9</sup> Contrast this mild stress with that experienced in a cold bath, which may actually cause in the adult a slight rise of body temperature because of overcompensation.

Recent observations<sup>10</sup> have indicated also that the regulation of

blood sugar is not perfected in the newborn. The baby's blood-sugar content may be as low as 70 or 45 mg.%, and it oscillates from day to day and even from hour to hour much more than that of the adult.

The way in which these regulatory mechanisms become gradually more effective in keeping steady the conditions in the fluid matrix is not understood. Mere exercise of the stabilizing process may result in the stability of later years, or it may be a consequence of the natural processes of growth and development. The existence of some defects in infants, however, indicates that others may be present that have been overlooked. Is the water content of the blood preserved as well in childhood as in the full-grown? Is the calcium and phosphorus relation maintained evenly in the early years when rickets is likely to appear? These and many other questions which call for answer indicate that the development of various corrective controls of the internal environment presents a largely neglected field of research. We need information in that field in order to judge more fairly the status of the growing child and to predict more reasonably what may be expected as time passes.

In later years the homeostatic regulators, repeatedly exercised and put to test, have a high degree of efficiency. And yet there are limitations to their ability to preserve a steady state in the fluid matrix. And that ability may well vary under different general conditions, during the normal and pathologic ups and downs of existence in an ordinary life cycle. Information on many of these points is not yet at hand; indeed, one of the objects of this lecture is to indicate where more knowledge is needed. It will be pertinent, therefore, to survey some of the stresses of homeostasis to which we are not uncommonly subjected, in order to learn how well the organism meets them and how much strain is imposed.

Perhaps the best approach to the problem which is before us is by way of considering what happens when we engage in prolonged and vigorous physical struggle. In various ways it tends to disturb the constancy of the fluid matrix. First, such struggle is accompanied by a large output of heat from the laboring muscles. The extra heat, if allowed to accumulate in the blood, would raise the body temperature to a disastrous degree. By action of the sympatho-adrenal system, however, sweating is stimulated, and more blood is sent through surface vessels which are cooled by evaporation of the sweat, and thus extra heat is eliminated. Again, as we have seen, a lasting muscular effort uses blood sugar, and the danger of hypoglycemia is avoided by sympatho-adrenal mobilization of sugar from its seclusion in the liver. And furthermore, there is danger from the development of non-volatile acid metabolites, especially lactic acid, which, if not burned to volatile carbonic acid and eliminated, may cause a markedly defective functioning of the very muscles which are active. As we have noted, through the agency of the

sympatho-adrenal system the heart is accelerated, the arterial pressure is raised, the spleen is constricted, and the red blood corpuscles, augmented in numbers, are sent at a faster pace to perform their task of conveying the needed oxygen. Now, we may engage in such a degree of muscular exercise that heat and acid are produced, and sugar is used, without affecting to a noteworthy degree the usual steady state of the fluid matrix. Or the exercise may be such as to raise the body temperature, shift the reaction of the blood markedly in the acid direction, and reduce the sugar percentage to a low level. It is when the temperature is elevated, let us say a degree or two F.; or when the oxygen delivery is not sufficient to burn the lactic acid at the rate of its production so that a noteworthy "oxygen-debt" is induced; or when the blood sugar is brought below, say, 70 mg. %—in spite of the protective mechanisms working, in each instance, to oppose the change—that the stress might be regarded as becoming excessive or *critical*, *i. e.*, inducing a breaking strain in the homeostatic mechanisms.

Exercise is clearly too complex and awkward a method of measuring the critical stress. Exposure to a standard high temperature in an atmosphere of standard humidity until the heat regulatory mechanism fails and the body temperature rises to a standard extent; or giving a standard dose of insulin and noting whether and when it overwhelms the compensatory reactions and produces signs of hypoglycemia; or breathing air which has a standard low oxygen content until adjustments of the respiration and circulation prove inadequate and indefinite symptoms of oxygen want appear—such would be relatively simple ways of learning the critical stresses of these distorting factors. I have put the suggestions in tentative form because experience might alter the methods—indeed, probably *would* alter the methods, which could be applied in measuring the critical stresses.

When we consider the fundamental importance of constancy in the fluid matrix of the body—how elaborate the physiologic devices for protecting it, how serviceable it is in liberating us from being subjected to external and internal conditions which would be disastrous, and how widespread the damaging effects when the constancy fails—when we consider these matters, we see the value of finding a reliable method to determine how efficient the protective devices are. Such a method would not only test the responsiveness of the sympatho-adrenal system as a regulator of the internal environment, but would also indicate the ability of the organs which are called into action by that system to play their rôle in the regulatory process. And it might be especially valuable in giving us information regarding habits and practices which alter, favorably or unfavorably, the homeostatic mechanisms.

Unfortunately, no intentional effort seems to have been directed toward the invention of means of measuring the critical stress which



various conditions might place upon the regulators of homeostasis. I have already suggested (see p. 9) exposure to insulin hypoglycemia, humid heat and low oxygen tension as possible ways of discovering the limits of the homeostatic regulators. Of these, insulin hypoglycemia seems least likely to be useful. The test would probably vary greatly with the nutritive state of the subject; the secondary effects—sweating and hunger, for example—would be partly subjective and would require considerable time for their development; and the analyses of blood sugar would be rather complicated and slow. Exposure to humid heat might likewise be difficult, because a special room or chamber, capable of being warmed and moistened to a standard degree, is necessary in order to make the test accurate. Of the three methods which have been mentioned the breathing of air containing a measured low percentage of oxygen appears to be the most readily applied. Because the sympatho-adrenal mechanism, as previously noted, works as a unit when strongly stimulated, a variety of tests is not demanded—one which is *reliable* is sufficient. And already experience has proved the possibility of using anoxemia as a measure of the adaptive adjustments of the organism, with objective indicators of the secondary disturbance when the stress becomes too great. Perhaps the greatest advantage of this means of evaluating the effectiveness of the preservers of constancy lies in the nature of the secondary disturbances; they are effects on the central nervous system, and consist in lessened ability to perform certain routine tasks. Since no system in the body is so sensitive as the brain to lack of oxygen, the anoxemia test is associated with an extraordinarily delicate indicator of the critical stress.

In principle, two ways of employing a method might be used to assay homeostatic efficiency. First, a standard severe stress, slightly more than that commonly endured, could be applied, and a study then made of the time which passes before a critical strain is reached. We may call this the method of *fixed stress*. Or the stress could be gradually increased until a critical or breaking strain is revealed, when the degree of the stress could be measured. This would be the method of *variable stress*. By either way it would be important to note not only the action of the sympatho-adrenal system as a coördinating agency, but also the action of the effector organs by which that system performs its functions. Only thus would one obtain evidence of where the weakness lies.

It has been interesting to find that both phases of the method of testing homeostasis by lack of oxygen were applied by a group of investigators who, during the World War, were charged with the problem of devising means for determining the physical fitness of pilots and the conditions which affect the ability of pilots to fly at high altitudes. A "Manual of the Medical Research Laboratory"<sup>11</sup> reports in detail the two ways of testing. The subject

was placed in a chamber in which the oxygen pressure was set at a low level (the method of fixed stress), or he had to rebreathe a certain volume of air (from which the carbon dioxide was continuously absorbed) until the oxygen pressure was more or less reduced (the method of variable stress). The latter proved the simpler and the more commonly useful means of making the examination. The subject, as a rule, did not experience any discomfort; indeed, he was usually quite unaware that the low oxygen tension had produced any change in his physical state, although by his responses he may have shown remarkable secondary effects on his nervous system.

During the period of rebreathing the secondary effects were determined by observers who recorded carefully and frequently the respiration, the pulse rate, the systolic and diastolic arterial pressures, as well as the performance of set tasks which demanded close attention and coördinated voluntary acts. When the subject's diastolic pressure fell sharply, or his heart, which had been accelerating, began to beat more slowly, or he lost consciousness as revealed by total failure to pay attention to his tasks or by fainting, the rebreathing was stopped. By analysis of the air from which he had been taking oxygen it was possible to estimate the altitude equivalent to the oxygen percentage which had proved too low for his compensatory reactions. Thus, with 21% oxygen at the start (representing sea level), 14% left in the apparatus at the time of the "break" would represent an elevation of about 10,000 feet; 10%, about 20,000 feet; and 8%, about 25,000.

In their reactions to this test men were found to vary in one of two general directions—toward fainting or toward failure of task-performance without fainting.<sup>12</sup> The physiologic aspects of the reaction included practically always a large increase in respiration. Of course, that is in addition to adjustment of the sympatho-adrenal system, unless dilation of the bronchioles be admitted as a change which would render heavy breathing more economical. The striking sympatho-adrenal adaptations which occurred in those who adjusted well to the diminishing oxygen tension include a faster pulse rate and a rise of systolic pressure. Also there is evidence that the heart puts forth a larger volume per beat. These changes may be regarded as serviceable in providing a faster blood flow and consequently a greater oxygen delivery to the most essential organs of the body (and those most sensitive to oxygen want), the heart and the brain. In other words, the changes are directed toward assuring homeostasis for those organs, even though other less immediately important organs in the body might suffer. Fainting is imminent when diastolic pressure begins to fall rapidly, or there is a drop in systolic pressure, or the heart beat becomes slow. In these circumstances the lower brain centers, controlling the heart and bloodvessels, appear to be the more sensitive indicators of failure to receive an adequate oxygen supply. In the non-fainting class

the blood pressure and pulse may remain fairly satisfactory, in spite of a low oxygen percentage, but the subject becomes stupidly unaware of his surroundings and of his own lapses of attention. Here the cortical functions of the brain are first to signal the deficit in the oxygen supply.

It seems probable that a standard for judging a critical stress from anoxemia could be found that would not require the test to be carried so far as to be near the edge of fainting or loss of consciousness. In most of the published records which carry the psychologists' observations, there are signs that, well before the circulatory changes have developed, the subject has begun to manifest characteristic disturbances of cerebral functions—such as confusion, wavering attention, clumsiness, delay and error in making the required motor responses. It is said, furthermore, that the reactions studied by the psychologist are the "best criteria as to the efficiency of the compensation." In the Government Manual (p. 87) the statement occurs, "As our work has progressed we have become more and more impressed with the perfectly definite effects following exposures to altitudes below 5000 feet." If such effects could be proved characteristic, and indicative of too great a stress, *i. e.*, a stress so great that the compensatory mechanisms are beginning to fail—even though 5000 feet would have to be much surpassed—a practical and simple test might be devised which would yield valuable information regarding the influence of common experiences on general bodily condition.

I have presented a sketch of the method of testing aviators because it has definitely proved that the efficacy of the adjusting apparatus in control of the fluid matrix can actually be evaluated. Indeed, the aviation tests have not only brought out clearly the quality of different types of physiologic organization, but also have disclosed evidence that bodily efficiency varies in a remarkably interesting manner at different times. A few illustrations will give point to these statements.

In some instances the observers found that there was "complete inefficiency" when the oxygen deficit marked an altitude as low as 6000 feet. Such subjects were in the main constitutionally inferior—often undersize, with flat chests, clammy, mottled hands and poor complexion. In the same class were men near middle age who had led a sedentary life and were overweight and of flabby musculature. Any functional defect of heart or bloodvessels was, quite understandably, the occasion for a low score. As the Manual (p. 32) remarks, "There is a certain range of greater or less breadth through which the external factors of the environment may be varied and yet be met by an automatic adjustment of the physiologic processes in the body which will preserve the vital balance of the mechanism. But beyond a certain point, specific for each organism, changes in the external condition will necessitate more radical alterations which will tax the compensating mechanisms to the

utmost capacity in order to prevent disaster. Theoretically the organism which has been called upon repeatedly to make a certain kind of adjustment (in this case supplying oxygen to meet a need) will be the one most capable of responding when an extraordinary demand is made. . . . Since physical exertion does increase the demand for oxygen it is to be expected that the organism which has been called upon to do physical work frequently will have acquired marked powers for compensating for oxygen want."

Although, as a rule, the athletic or physically fit person is best able to meet the exigencies of anoxemia, he himself may show noteworthy variations of response to low oxygen percentages, according to his "condition." Thus during a cold, or after a recent illness, or when the body has been damaged by unhygienic living, or weakened by inactivity or by worry or dissipation or loss of sleep, the capacity for endurance of oxygen deficiency is apt to be reduced. Then as the oxygen in the rebreathed air becomes less there is an earlier onset of inefficiency than would occur if the subject were quite fit. For example, one of the subjects, often tested and proved to be exceptionally hardy, was brought on a particular day to an oxygen level equivalent to an elevation of 22,000 feet, and was kept there for 15 minutes with hardly any effect on his general responsiveness. That evening he dined with friends, drank a moderate amount of alcohol, and went to bed late. The next morning he felt a little giddy and had a slight headache. Then, when tested at 18,000 feet, he became cyanotic and was wholly incapable of meeting the psychologic tests. Only by prompt administration of oxygen was he prevented from fainting.

It is hardly necessary to point out that this mode of estimating the capacity of the sympatho-adrenal apparatus (and its subservient organs) to meet certain standard requirements has given us quantitative information regarding "fitness," and regarding the circumstances which affect "fitness," that we have never before possessed. It is not necessary to use the vague phrases "being in good condition" or "being in poor condition," if a test can express graphically and in fairly accurate terms what those phrases mean. The possibility of securing that degree of exactness in a realm of medical observation where judgment has been uncertain and description indefinite would amply justify an effort to simplify the aviation tests so that they could be applied reliably to medical cases without too great expenditure of time. Or it is conceivable that some other ready way could be found for judging sympatho-adrenal efficiency. At this point I wish merely to emphasize the importance of establishing a satisfactory uncomplicated method of assaying that efficiency. If that could be done we should have a means of learning how all sorts of human experience affect the fundamental factors which determine homeostasis. A vast territory, enticing for biologic and medical exploration, would be disclosed. We should have to learn how steady are the steady states and where the critical

stress is found, not only in normal individuals, but also in individuals at various developmental epochs and during various disorders. Childhood, adolescence and old age, the exacting periods of puberty and the climacteric, prolonged labor, fatigue, the demands of school, the values of different sorts of training—all these and many other conditions (besides infection and insomnia, worry and dissipation, already mentioned) could be made to tell their influence on the agencies which maintain uniformity in the fluid matrix. Indeed, the whole gamut of human diseases might be studied from this point of view.

The main objectives which I have had in mind while preparing this lecture are two: I have wished to rouse interest in the stability of our internal environment and in the admirable regulatory mechanisms which maintain stability and which are found in the functioning of the sympatho-adrenal system; and I wished also to indicate the importance of a means of estimating the efficacy of that system as a regulator of bodily stabilization. Unfortunately I have not been able to bring to you an account of a well-tried method of discovering the critical stresses in homeostasis, a criterion for judging the degree of perfection of the corrective and preservative devices in our physiologic economy which assure us freedom for our more interesting and important activities. But am I right in saying "unfortunately"? Does not the chase often yield quite as much satisfaction as the quarry? Of our "more interesting and important activities" is not the quest for illuminating facts among the choicest and most admirable? Perhaps I had better say "fortunately" there is much significant and rewarding research ahead of us, research needed for the relief of man's estate. It would be most gratifying if any hints I may have offered would serve as a stimulus to fresh endeavors to bring us new knowledge and new power.

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## THE RELATION OF DENTISTRY TO MEDICINE.\*

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DENTISTRY, or stomatology, as some now prefer to call it, is gradually being given the standing of an important junior member of the medical family. While its interests have been largely concentrated, during its comparatively short life as an organized profession, in the field of mechanical and surgical therapy, of late it is being realized that many of its problems lie directly in the field of general medicine. Its course as a member of the medical family will be that of any other well-conducted junior—it will follow in the footsteps of its elders, at least such footsteps as have led forward, and it will continue, in its practice, in its education and in its research to be guided by the experience of those who have preceded it on this course of professional development.

My theme today—the relation of dentistry to medicine—is a phase of progress in the history of medical art and science. Dentistry is one of the subdivisions of the healing art and occupies in practice a relation to the main body of medicine essentially like that of otology, laryngology and ophthalmology. Like all these, it springs from the main trunk of general medical knowledge and experience.

*Gradual Recognition of Teeth as Organs.* The necessity for the ministrations which the dentist now gives is as old as the teeth themselves, just as—if we are to go back to origins—the necessity for the ophthalmologist was determined by the occurrence of the eye. But by one of the most singular aberrations of the human mind, extending over centuries, teeth were long regarded as if they were something extraneous to the body—something essentially inanimate presumably because of lack of a visible capacity to repair themselves. They were thought to be a sort of added convenience or mechanism—as though they were not produced by the body in which they occurred, but were added to it. Teeth had the rank and standing of mechanical appliances, existing largely for the purpose of mastication, with adornment also playing an important rôle. Had it not been for toothache, which brought poignant evidence that they were not inanimate, teeth never would have been forced upon our attention.

*Dentists Admitted to Medical Ranks.* Perhaps it was this anomalous status of the teeth which accounted for the no less anomalous status so long occupied by the dentist. Over extended periods he shared in the dubious classification of the barber-surgeon union.

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A later stage was that of the tooth-puller, when he was confused in the public mind with the traveling charlatan and the local jack-of-all-trades. For a century or more he lived in a no-man's land between a profession and a trade. Dentists, even in our own time, are being admitted very slowly and not without resistance, to the general company of physicians and surgeons. Within the lifetime of those present the dentist has continued to be regarded in some quarters as a mechanic and his occupation as a manual craft. It is not 6 months since a learned professor at my own university coupled dentistry and plumbing as the two leading contributions of America to culture. It is difficult for the dentist to feel adequately flattered by the collocation.

*Undue Specialization.* On the threshold of the medical profession the dentist meets a new danger from the undue specialization that has been attacking in epidemic proportions the entire healing art, separating it into formal divisions and breaking it up into a number of water-tight compartments.

Specialization was in its origin unavoidable. It was made necessary by the expansion of the field of knowledge. Since the death of Roger Bacon, in 1294, no one mind has been able to embrace the whole of science. Subdivisions and specialization were made necessary by the rapid and immense increase in nearly all fields of knowledge. As the aggregations of facts, accumulating at accelerated speed, piled up before the scientist, in quantities so vast that they swamped the mind, they led to increased specialization and resulted in many scientists becoming wholly immersed in minor subdivisions and specialties.

Our zeal for specialization in all directions has carried us to extremes. The banker has sometimes tried to conduct his affairs as if they formed a water-tight compartment and as if finance were independent of business. The physicist, the chemist, the economist have essayed to live within a tight fence where other specialists might not intrude. Medicine has broken its province into a score of principalities. Even the restricted field of dentistry has fallen into the current error; it has not merely set up its own boundaries, but has split its enclosure into subdivisions—prosthetics, orthodontia, periodontia, oral surgery, etc.

*Medical Subdivision.* In course of time the law has allotted to each its own portion of the body, and the mouth with its complement of teeth has become the legal domain of the dentist. The rest of the body remains as yet the domain of general medicine, but whether the various specialties of medicine will be content, whether they will not each demand its "pound of flesh," its segment of the body, to be its proper province, defined and apportioned to it by legal enactment—that is a question. It is no great feat of imagination to see the body all apportioned out and allocated, organ by organ, part by part, to the ophthalmologists, orthopedists,

laryngologists, cardiologists, gastro-enterologists, gynecologists, etc. How far would such division go? To what lengths would the jealousy of legal and medical rights carry our energetic specialists? One shrinks from the vision and wonders whether the ancient writ of *Habeas Corpus* would not have to be revised to read *Habeas Nares*, *Habeas Cordum*, *Habeas Pedem*!

No! Specialization will not go to such lengths; common sense will intervene. It is possible to make legal division of the body, but Nature knows none. Her consent has not been given. No legal barrier can stop the toxin from an infected tooth spreading to the heart and interfering in its action, or to the joints and stimulating arthritis, or to the eye and affecting vision, or prevent a dysfunctioning heart from affecting unfavorably other structures. All specialization, whether it affects dentistry and general medicine or as it affects the various subdivisions of both, can be justified, not as a means of separation, but only as it aids and facilitates coöperation.

*The Status of Dentistry.* Dentistry has marched, step by step, to a place where it must be regarded in general as belonging to medicine. The status cannot yet be regarded, however, as wholly satisfactory—neither on the side of professional practice, nor yet as regards professional education. This is partly due to the action of the medical authorities of another day in refusing to admit dental subjects to the medical curriculum. The consequence was the establishment of separate dental schools with their own curricula and separate professional organizations. It is undeniable that the independent course then taken by the dentists and their attitude of self-sufficiency accounted in some measure for a certain aloofness of manner on the part of the medical profession. Separate dental schools at any rate came into being, not usually on equal scientific and intellectual level with the medical schools of the same period, and sometimes on a level decidedly lower. With the passage of time this gap is in process of being closed. The requirements for admission at the better dental schools and the general requirements for the dental degree are not inferior to those for the medical degree. Nor is the dental student at graduation less well prepared, but, on the contrary, rather better than his medical confrère, for the immediate practical problems of practice.

*Dental and Medical Students.* In general, there is visible today a growing affinity of the curricula of dental and medical schools. In some dental schools the work of the first 2 years of the course is identical in subjects taken and not inferior in quality to that of the first 2 years of the medical course and is frequently taken in the same lecture rooms and under the same instructors. The routine of lecture, of study and of laboratory work, and the personal relations set up with fellow medical students and professors tend to establish



and maintain common standards, lifelong habits of thought and bonds of fellowship.

On the medical side also there are tendencies toward closer relations in the curriculum. At least one medical school has moved to establish within its regular course, requirements in the dental field similar to the requirements set up in ophthalmology, otology and laryngology. This will further broaden the common ground and will prepare the way for a common footing in hospital service when, as is inevitable, it becomes the general practice of hospitals to have dental interns. In at least 2 hospitals with which I am familiar this has already come about.

*For a Uniform Curriculum.* The relation to medicine will be more satisfactory when the requirements for entrance to the dental profession are more uniform and when all dental schools adopt and enforce the standard of the leaders. That condition is rapidly being brought about. (This desirable goal has been made more attainable by the aid of the Carnegie Corporation, enabling the American Association of Dental Schools to make a study of the dental curriculum with regard to the requirements of the profession. As the same requirements and standards are applied to dentistry as to other specialties of medicine we shall find the old *odium medicum* disappearing.)

Conversely, on the side of the medical schools, there is an approach to dental subjects which indicates a more sympathetic understanding, and it is a matter of congratulation, alike to the medical and the dental faculties, that medical students show a keen and decided interest in dental subjects—an interest extending to the point of requesting an increase in the number of sessions devoted to dental problems.

*Dr. Thayer on Interdependence.* This whole relationship has been a matter of serious interest to many of the best minds of the profession. For example, the late Dr. William S. Thayer, one of the most distinguished and beloved members of the profession of his generation, as inspiring a friend to many of you as he was to me, in a report on the Harvard Dental School wrote as follows:

“The ophthalmologist and the physician meet on common ground: they are members of the same medical societies. Their subjects are discussed at common meetings. The dentist and the physician do not meet on the same common ground. This is unfortunate for the physician, for the dentist and for the patient. The circumstance that the requirements for admission to dental schools have been lower, and the circumstance that the amount of general and medical education demanded of the dentist has been less than that demanded of the physician and surgeon, have worked to place the dentist at a disadvantage in the medical and general community. This has not only been a disadvantage to the dentist, it has been a

very real disadvantage to the medical profession. It is, we believe, of importance to medicine that the time may come when . . . dentistry will be, as it should be eventually, one of the specialties of surgery . . .” And he closes by saying: “As the years go by, the importance of that branch of surgery practised by the dentist becomes more and more evident, and the interdependence of dentistry and the other branches of the art of medicine and surgery clearer . . .”

*Hospital Service.* As has already been suggested, a further step of progress will be made when dentists are regularly to be found in our hospitals as residents and interns. Such a step is desirable in the interests of the general health, because hospitals are the true mixing and testing grounds for the various groups of practitioners and specialists, true medical melting pots.

Perhaps even more important is the development of dental diagnosticians—a forward step proposed by President Lowell, of Harvard, strongly advocated by him, and under serious consideration in some of our hospitals. No one who has had experience in ward walks can have failed to realize how valuable in some cases a dental diagnosis may be. Although the subject of the mouth as a primary focus of systemic disease has rather overshadowed other aspects of the whole problem, we are now beginning to realize that certain diseases display early symptoms in the mouth—to the extent that we may even call the mouth a barometer of body health. Certainly no case can be regarded as thoroughly studied until an accurate and complete survey of mouth and teeth has been made. If this be true, the more effective and closer the coöperation of dentist and physician becomes, the better will be the service rendered the patient.

In all the professional relations in which dentists and physicians meet, in classroom, hospital clinics, as well as the routine of practice, the relations tend to grow closer and the exchange more reciprocal and coöperative. This is because the basis of common interests, common knowledge and common training grows constantly broader and is better understood.

*Research.* Nowhere is this plainer, nowhere is coöperative exchange more fully taken for granted and more imperative than in the field of research. Every investigator learns early in his experience that research cannot be conducted on the water-tight compartment basis. It is constantly crossing lines of technical, departmental and professional knowledge, and as fast as it expands it draws men of different faculties and diverse sections of science into ever closer coöperation.

This inevitable interrelation is illustrated wherever research, whether it begins in the dental or the medical field, is being carried on. For example, in one of our dental schools considerable research

is being conducted in the three major fields of dental disease: caries, pyorrhea and malocclusion. The field of caries demands especial attention because it is the most universal and the most familiar of all human ailments of our day. It is also an ailment which brings in its train many *sequelæ* to which medical men must direct their attention. Caries, therefore, of necessity interests medical men.

*Research on Caries.* In the school to which I refer there are no fewer than 8 pieces of research being carried on upon different phases of caries. This is natural for the reason that, as everyone knows, there is a wide difference of opinion as to the cause of the ailment. Since the days of Miller, when there was general acceptance of the view that caries was a germ disease and that all we had to do was to find and isolate the bacillus, we have gone through a series of changes of opinion. While some are still pursuing the bacteriologic trail, others have become equally convinced that the cause lies in nutrition. Within the field of diet again we have a number of more or less conflicting theories.

*Interrelation in Research.* No matter what theory the investigator in this subject of dental caries adopts, he will find that his work will carry him immediately across the lines of the established fields of medicine. For example, the study of the vitamin and mineral deficiencies will bring him immediately into close relations with active workers in several fields of research and, particularly if he is wise and fortunate, into cordial collaboration with the men who work in biochemistry. Again, as soon as he begins to study the effects of caries upon dental tissues, he will find himself in the field of pathology and coöperating with men in the pathologic department of the medical school. Let him turn to the effects of the *Bacillus acidophilus*, and he is at one step in the field of the bacteriologist and is again in close coöperation with the bacteriologic division of his medical school.

If he has gone further afield, and has become attracted by the effects of the endocrine glands as predisposing to caries, he will not advance far without being in coöperative relations with the men similarly engaged in the department of anatomy or surgery.

It is plain, therefore, that even within this single field of research into our most commonplace ailment, caries, we shall be involved in all four of the major departments of medicine and shall come, if we are fortunate, into happy coöperation with the men doing similar work in the departments of pathology, bacteriology, anatomy and biochemistry.

*Interrelations in the Study of Malocclusion.* The other divisions in which dental research is being carried on—certainly in one school, and I think perhaps in many others—lead equally to the same result, that is, to the impossibility of any effective research which

does not cross the boundaries of some, if not all, of the major divisions of medicine, and does not involve interrelations of the closest kind if effective work is to be done. For example, take the work which has been continued for some years by one of my colleagues in malocclusion, which leads directly to the study of bone growth. Ingenious forms of investigation in this field have led to the use of madder to reveal the modes of growth in bone, especially under various forms of strain. Mechanical means, with which all orthodontists are familiar, for bringing about changes and for stimulating growth at certain points in the jaw, have made it particularly desirable to know how and just where in the structure of the jaw these mechanical appliances bring about or stimulate the deposition of new bone. This study, continued over a number of years with the aid of animal experiments where both mechanical appliances and madder feeding could be made use of, has not only produced highly interesting and illuminating results; it has given a demonstration equally convincing for our immediate thesis. It has shown how indispensable is coöperation of more than one department of medicine in prosecuting such an inquiry. For example: Starting in the department of pharmacology, very early in the inquiry the investigator's work drew him into the department of physiology; at a stage not much later he found himself working also with the departments of anatomy and chemistry.

*For Closer Coöperation.* This is typical, and so far as I know universal, in all our research work. We can do effective research only by the fullest and freest coöperation of practically all the departments of medicine. These examples from the research laboratory will tend, I think, to corroborate and establish the reasoning drawn from the fields of dental education, from daily practice and from the clinics that holds that the line of progress for dentistry and medicine alike is that of interdependence and close coöperation. It might be said of the various divisions and specialties of medicine, as it was said by St. Paul of old, "No man liveth unto himself." Isolation is impossible, where it is not suicidal, and the progress of each is to the advantage of all.

**Conclusion.** Sound progress of the dental division of medicine is one which ought to be welcomed by every thoughtful physician, because it means lifting one more division of the whole practice of medicine onto a more intelligent, a more scientific and a more efficient basis. We are all, whether we will or no, part of the same body of learning and practice. None of us can be depressed or unworthy without affecting unfavorably the whole body. None of us can make advances in knowledge or skill or character without once more lifting the level of the whole, and so the medical profession at large will find it is to its interest and to its credit to foster every advance that is made by the dental branch of the healing art.

# DETERMINATION OF THE PHAGOCYTTIC POWER OF WHOLE BLOOD OR PLASMA-LEUKOCYTE MIXTURES FOR CLINICAL OR EXPERIMENTAL PURPOSES.\*

## DESCRIPTION OF AN IMPROVED METHOD, WITH REPRESENTATIVE FINDINGS.

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THE efficiency of the blood in clearing itself of bacterial invaders under given conditions is obviously a factor which enters intimately into many problems of infectious disease. Will a given infection spread or be self-limited; will therapeutic serum help, and, if so, what serum and in what dosage; has the patient's normal resistance become reinforced as a result of vaccination or infection? Any of these questions could obviously be considered more intelligently if the ability of the patient's blood stream to clear itself of the bacteria in question could be determined.

Under certain circumstances direct determination of the bactericidal power of whole blood is practicable. Indeed, studies by Robertson and others<sup>1,2</sup> of the pneumococcidal power of whole blood have greatly illumined many problems of pneumococcus infection in man and lower animals. However, attempts to measure the bactericidal power of the blood against, for instance, staphylococci and certain streptococci have been by no means so successful as against pneumococci.

Phagocytosis is the principal means by which bacteria are cleared from the blood stream. Direct bactericidal action by sensitizer and complement is known to occur with only a few bacteria; for the majority of pathogens, phagocytosis is the only known means of destruction. A simple quantitative method of estimating the phagocytic power of whole blood should, then, have many uses.†

\* This investigation has been aided by a grant from the Faculty Research Committee of the University of Pennsylvania.

† In clearing bacteria from the circulating blood phagocytosis by macrophages in liver, spleen, lung and elsewhere is probably of equal or greater importance than phagocytosis by circulating polymorphonuclear leukocytes.<sup>3,4</sup> Macrophages and polymorphonuclears have been shown to respond similarly to phagocytosis-promoting substances, however, under a variety of circumstances.<sup>5</sup> The phagocytic power of the polymorphonuclear leukocytes in blood, we believe, therefore, can be used at least as an approximate indication of the total clearing power of the blood.

Among the earlier studies of phagocytosis which have become classics are the brilliant experiments of Wright and Douglas,<sup>6</sup> which first disclosed the normal phagocytosis-promoting substances named by these authors "opsonins." It is strange, however, that the essential technique used in these pioneer experiments should have persisted as the current clinical method of estimating phagocytic power for the succeeding 30 years.<sup>7,8,9</sup> To appreciate the confusion introduced through the imperfections of the Wright technique requires merely a study of the literature.<sup>10</sup> Zinsser and Bayne-Jones say of it:<sup>9</sup> "Measurements of opsonic indices are subject to so much experimental variation that they cannot be done with sufficient accuracy in clinical laboratories without an amount of labor that renders them useless as practical procedures."

The procedure described below was developed in the hope of providing a simple, accurate and practicable measure of phagocytic power. We are finding it useful.

**Procedure.** *Anticoagulant.* Prepare a stock solution of purified heparin (Hynson, Westcott and Dunning) by dissolving 25 mg. in 5 cc. of 0.85% sodium chlorid solution. This solution can be sterilized by autoclaving. The amount of the freshly prepared solution we have used with 1 cc. of human blood is 0.05 cc. of the stock solution; for dog blood, 0.1 cc. of the stock solution has been used. The presence of the anticoagulants which precipitate calcium is known to interfere with phagocytosis.<sup>11,10</sup> We have not detected any interference with phagocytosis by purified heparin, or for that matter in using the less expensive unpurified product.

*Preparation of Bacterial Suspension.* A reproducible suspension of evenly suspended microorganisms is desired. In work with pneumococci we have used 19-hour cultures in infusion broth adjusted before autoclaving to pH = 8 with phosphate buffer. The bacteria were washed twice and resuspended in buffered broth. A bacterial count has then been made in a Petroff-Hausser counting chamber, and the density adjusted to about 6 billion organisms per cc. With bacteria that are more readily phagocytized than smooth pneumococci, less dense suspensions are used.

*The Agitator.* Some means of securing a uniform and reproducible amount of agitation of the phagocytic mixture is necessary for precise work. A suitable apparatus, which has been made available by the A. H. Thomas Company (Fig. 1), consists of a copper water bath containing a movable copper test-tube rack, a universal motor for 110 volts a.c. or d.c., and a gas microburner with attached stopcock mounted on a baseboard with switch and necessary wiring connections. The motor is geared to swing the movable test-tube rack to and fro approximately 280 times per minute. The rack takes 16 tubes, 15 by 85 mm. By means of the gas burner with stopcock for adjustment of the gas flow, a temperature of approximately 37° C. can be maintained in the water bath. Clips are provided within the bath for conveniently holding a suitable thermometer.

*The Test.* 1. Place 0.05 cc. of stock solution of purified heparin in a test tube for each cc. of blood to be obtained.

2. Obtain blood by venous puncture and place in tube containing the heparin. Mix gently.

3. Place 0.5 or 1 cc. of heparinized blood in a short test tube, 15 by 85 mm., and place in agitator bath. The water in the bath should be between 37° and 38° C.

4. Add 0.1 cc. of bacterial suspension to the blood; note time and mix quickly by gentle agitation. Start agitator.

5. At regular intervals remove by means of capillary pipette sufficient blood for making a smear in the same way as is usual for differential counts of blood. This can be done without stopping the agitator by dipping the pipette in the blood and removing quickly. A new pipette should be used for each interval. The slides should be perfectly clean and the ones used for spreading the film should have the corners cut off, so that the width of the film will be somewhat smaller than the width of the slide. This is done so that the edges of the film may be more easily examined. The interval of time that has proven satisfactory in most of our studies has been 3 minutes. In some instances where phagocytosis is rapid, 1-minute intervals were used. The smears should be thin enough to dry rapidly.

6. Fix the smears in methyl alcohol for 10 minutes.

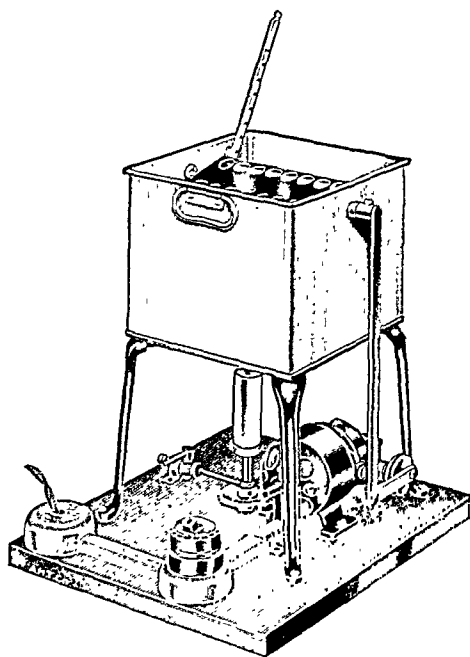


FIG. 1.—Shaker for phagocytosis tests.

7. Use Giemsa stain, so adjusted with a weak solution of sodium carbonate that the bacteria and cells stain well. It is advisable to make a few extra slides at the end of the test for the purpose of testing the stain before staining the test slides. Other suitable blood stains may, of course, be used.

8. When making smears by the method just described, it will be found that the neutrophils are much more numerous along the edge of the film. This arrangement of the cells facilitates the examination by making it easy to locate the cells, and prevents the possibility of counting the same cell twice. The smear is examined by focusing the edge at one end and examining the cells found along or near the edge, always moving the slide in one direction. If sufficient cells are not found the other edge should be examined. The cells should be classified as positive or negative for phagocytosis. The results are expressed in terms of percentage of positive cells. At least 100 cells should be classified. Cells which are so clumped that their cyto-

plasm cannot be easily outlined or cells which are broken up or degenerated should be disregarded. Only cells which have organisms within their cytoplasm should be considered positive. When bacteria are merely adherent to the cell or appear partly ingested, the cell should be classed as negative.

9. Curves can be obtained by plotting the percentage of positive cells against the time intervals.

*Test for Phagocytosis by Plasma-leukocyte and Serum-leukocyte Mixtures.* Tests with plasma-leukocyte and serum-leukocyte mixtures are conducted as outlined above for whole blood. The only special feature requiring detailed discussion is the collection of the leukocytes.

*A Method of Collecting Human Leukocytes.* Collection of leukocytes by the "buffy-coat" method from small amounts of blood\* did not satisfy our requirements as to yield of leukocytes and absence of erythrocytes. It seemed possible that, allowing the blood to sediment, the erythrocytes would settle first, leaving the leukocytes above, and that by removing the plasma at the proper time, it would contain the leukocytes with very few erythrocytes. This was first tried with citrated blood. The blood was removed by venous puncture and 0.5 cc. of 3% sodium citrate was added to each 5 cc. of blood. A total white cell count was made. Several sedimentation tubes were filled with blood and were allowed to settle. At half-hour intervals the plasma was removed and the number of leukocytes in the plasma removed was counted: To our surprise the number per c.mm. in the plasma at the end of the first period not only equaled the original count, but far exceeded it. This was an unexpected phenomenon. For fear of technical error, more tests were conducted with similar results. Some of these are shown in Table 1.

TABLE 1.—CONCENTRATION OF LEUKOCYTES IN PLASMA LAYER ABOVE SEDIMENTING ERYTHROCYTES.

Blood sample A: leukocyte count, 5200.			Blood sample B: leukocyte count, 5100		
Interval, hr.	Height of plasma taken, mm.	Leukocyte count.	Interval, hr.	Height of plasma taken, mm.	Leukocyte count.
$\frac{1}{2}$	8	12,000	$\frac{1}{2}$	4	16,450
1	10	14,400	1	5	12,350
$1\frac{1}{2}$	6	10,700	$1\frac{1}{2}$	6	11,500
2	5	9,000	2	4	9,000
$2\frac{1}{2}$	5	6,000	$2\frac{1}{2}$	3	5,000
3	5	3,400	3	$2\frac{1}{2}$	1,000

Mixed plasma A: Total plasma recovered, 2 cc.; leukocyte count on mixed plasma, 10,000; percentage of leukocytes present in whole blood recovered in plasma, 38%.

Mixed plasma B: Total plasma recovered, 3 cc.; leukocyte count on mixed plasma, 7000; percentage of leukocytes present in whole blood recovered in plasma, 41%.

To check these observations in another way, a sample of horse blood was obtained by venous puncture and placed in a small tube. There was marked sedimentation of the erythrocytes before coagulation took place. The clot was then fixed, sectioned and stained with hematoxylin and eosin. Examination of the sections showed a marked increase of leukocytes in the top portion of the clot as compared with the bottom portion; the top portion was, of course, relatively free from erythrocytes.

It seems that this phenomenon may be explained by the fact that the erythrocytes have a higher specific gravity and, therefore, settle more

\* However, a satisfactory method of obtaining a "leukocytic cream" from larger volumes of blood has recently been described by Strumia.<sup>12</sup>



rapidly than the leukocytes, thus leaving the leukocytes in the upper strata of plasma. If the erythrocytes settle rapidly, the displacement of the plasma at the bottom by the cells will cause currents sufficient to carry some of the leukocytes upward and thus increase their number in the supernatant plasma. When the settling of cells is slowed or stopped, the leukocytes then settle to form a layer on top of the red cells (so-called "buffy coat").

Our earlier observations were made with blood from clinic patients who no doubt were not normal and had increased sedimentation rates of their erythrocytes. Subsequent studies with blood from normal individuals showed the same phenomenon, although less pronounced, and the amount of plasma-leukocyte mixture removed was too small to be of practical value. It then became necessary to accelerate the sedimentation of the erythrocytes and thereby allow the removal of more plasma-leukocyte mixture in order to increase the number of leukocytes recovered.

This was accomplished by removing a little over one-half of the erythrocytes by the following method: Place blood in test tube and centrifuge at moderate speed for 5 or 6 minutes; remove cells from the bottom by means of a capillary tube so bent that one end can be inserted in the tube to the bottom; the other end will reach a few inches below the bottom of the tube on the outside; by suction a syphon is established and the cells removed drop by drop until less than one-half remain. The tube is then removed and the remaining cells are resuspended by tipping back and forth gently. This blood will now settle rapidly; consequently more plasma and leukocytes can be recovered.

All the factors which influence the sedimentation rate<sup>13</sup> naturally influence this phenomenon and the collection of leukocytes by this method. Those accelerating sedimentation, such as body temperature and tilting of the sedimentation tube, can be used to advantage. Sedimentation should be started as soon as possible after withdrawal of the blood. Having the leukocytes in a high column of plasma facilitates their removal, as it does not necessitate the removal of plasma close to the erythrocyte zone. We have found it advisable to have the column of blood at least 100 mm. high; but this, of course, will vary according to the amount of blood available and the number of leukocytes desired.

The plasma so collected contains leukocytes and platelets with very few erythrocytes. By centrifugalizing slowly for a few minutes the majority of the leukocytes may be thrown down; the majority of the platelets may then be removed with the supernatant plasma. The leukocytes are carefully resuspended in the desired volume of suspending medium.

We have used as anticoagulants sodium citrate, sodium and potassium oxalate and heparin with good results. If the leukocytes are intended for phagocytosis, heparin should be used, or else the leukocytes should be carefully washed before using. Attempts to recover leukocytes from defibrinated blood by this method have not been particularly successful.

*Method of Collecting Leukocytes.* The following is an outline of a method for collecting human leukocytes based on the facts discussed:

1. Obtain blood by venous puncture. The amount will depend upon the number of cells desired.
2. Place in tube containing anticoagulant.
3. Centrifuge at moderate speed.
4. Remove a little over one-half of the erythrocytes from the bottom of the tube by means of capillary tube, or in any manner which will not disturb the "buffy coat." If the blood is from an anemic person or has an accelerated sedimentation rate this step can be omitted.
5. Gently mix the remaining cells with the plasma.
6. Place the blood in a tube of such diameter that the column will be at least 100 mm. high.

7. Place the tube in incubator and incline slightly.

8. Remove the plasma from top with capillary pipette at end of  $\frac{1}{2}$  and 1 hour. The time of collection may be varied according to the rate of sedimentation. If it is necessary to obtain as many leukocytes as possible, the collection should extend until no more plasma is available.

9. A total and differential white cell count may be made if it is necessary to determine the number and kind of leukocytes recovered.

The number of leukocytes recovered by this method depends: (1) Upon the number of leukocytes present in the original sample of blood; and (2) on the factors influencing the sedimentation rate of the erythrocytes. We have been successful in most cases in recovering from 20 to 60% of the leukocytes present in the original sample. In all cases we have been able to recover far more leukocytes which are relatively free from associated erythrocytes than we could expect to by the "buffy coat" method.

**Representative Data on the Phagocytic Power of Whole Blood and of Plasma-leukocyte Mixtures.** Data obtained by these methods (Fig. 2) are plotted as rate curves expressing the percentage of neutrophils which have phagocytized in the successive time intervals.

*Relative Resistance to Phagocytosis of Different Bacterial Strains.* Resistance to phagocytosis is known to be a major factor in determining virulence, for instance, of pneumococci. In the experiment recorded in Fig. 2, A, 1-cc. samples of heparinized human blood were mixed with 0.1 cc. of twice-washed pneumococcus suspension containing in each case approximately 600 million microorganisms. Four strains of pneumococci were used, *i. e.*, fully virulent Types I and II smooth strains (I S and II S), a laboratory strain of Type III smooth of moderate virulence (III S), and an avirulent rough strain originally derived from Type I (I R). It is evident that phagocytosis of Type I S was negligibly slight, of Type II S little more, of Type III S moderate and of the rough strain rapid and extensive.

*Titration of Phagocytosis-promoting Action of Therapeutic Serum.* In the experiment recorded in Fig. 2, B, the phagocytosis-promoting action of a therapeutic antipneumococcus horse serum\* against the same virulent strain of Type I S was titrated. Serial dilutions of the horse serum were added to 1-cc. portions of human blood so as to give the final dilutions of horse serum shown in the figure; 600 million twice-washed pneumococci were added to each portion of blood. It is clear that the serum in dilutions of 1 to 200 and 1 to 400 had little or no effect on phagocytosis, that in a dilution of 1 to 100 a slight phagocytic response was obtained, and that in dilutions of 1 to 25 and 1 to 50 the phagocytosis-promoting action was very effective.

*Inhibition of Phagocytosis.* The carbohydrate capsular materials of pneumococci are known to have an extremely important effect in inhibiting phagocytosis.<sup>14</sup> This effect is a major factor in the

\* For the horse serum we are indebted to the Mulford Laboratories of Sharp & Dohme.

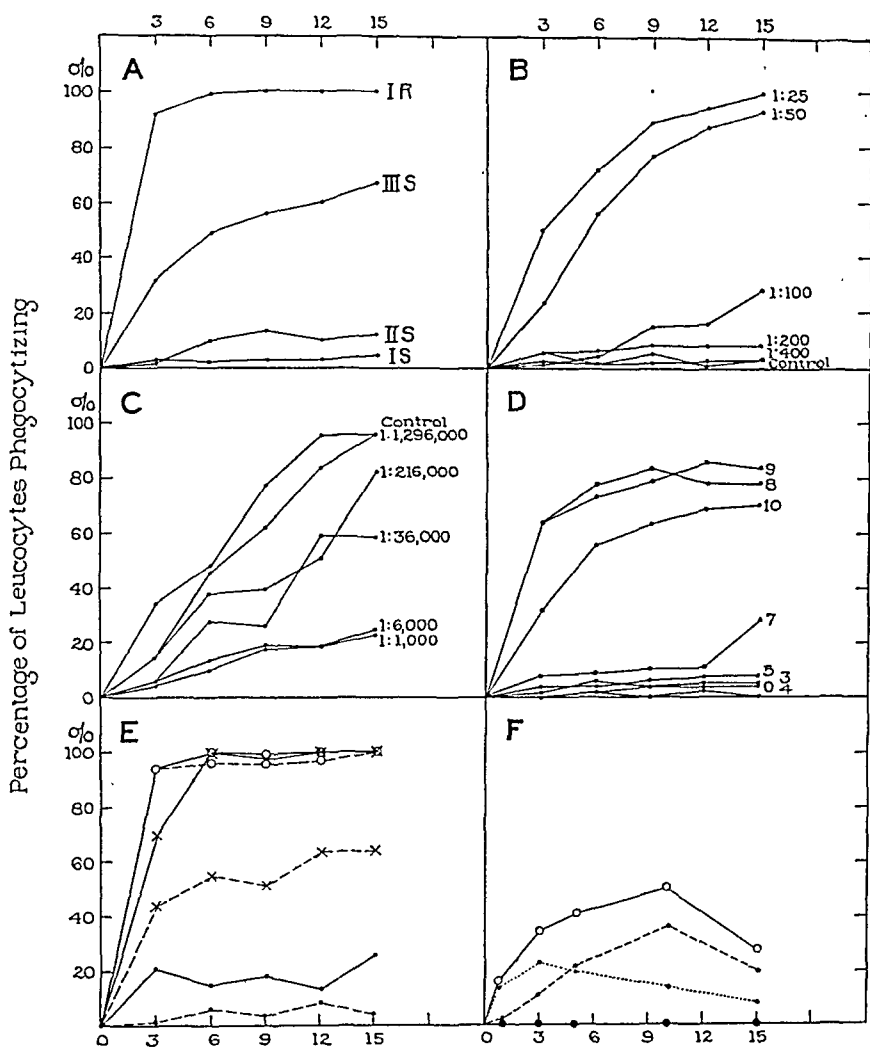


FIG. 2.—A through E, Rates of phagocytosis of bacteria by polymorphonuclear leucocytes in whole blood. A, Human blood. Pneumococci of Types I, II and III, smooth, and rough derived from Type I; 600 million twice-washed pneumococci in buffered broth added to each 1-cc. portion of heparinized blood. B, Human blood (1 cc.) plus 0.1 cc. of serial dilutions of therapeutic antipneumococcus horse serum; final dilutions of horse serum given in figure; 600 million twice-washed Type IS pneumococci in buffered broth added to each tube. C, Human blood containing antipneumococcus horse serum added to a suspension of Type IS pneumococcus containing serial dilutions of Type I S.S.S. Dilution of horse serum in the final mixture, 1 to 50. The initial dilutions of S.S.S. are indicated on the graph; to obtain dilutions in the final mixture multiply by 13. D, Dog blood. Numerals indicate days following infection with Type I pneumococcus—600 million twice-washed pneumococci in buffered broth added to 1 cc. of blood. E, Blood of patient with eosinophilia. Solid lines, neutrophils; broken lines, eosinophils. Open circles, *Staphylococcus aureus*, heavy suspension. Solid circles, pneumococcus Type IS; 600 million pneumococci added to each cc. of heparinized blood. Crosses, pneumococcus Type IS plus antipneumococcus horse serum; dilution of horse serum in the original mixture, 1 to 75. F, Human plasma-leukocyte mixture (Type O), plus erythrocytes (Type A); 50 million erythrocytes added to 0.5 cc. of plasma containing 18 million leukocytes. Dotted line, leukocytes containing stainable erythrocytes. Broken line, leukocytes containing vacuoles. Solid line, sum of leukocytes containing stainable erythrocytes and vacuoles. Solid circles along baseline, same plasma-leukocyte mixture plus Type O erythrocytes; no phagocytosis.

so-called "aggressive action" of pneumococci and other bacteria.<sup>15</sup> In the experiment shown in Fig. 2, *C*, such an inhibitory action is shown. The therapeutic horse serum was added to portions of the same human blood used in Fig. 2, *B*, so as to give a dilution of 1 to 50 horse serum in the final mixture. Dilutions of deacetylated Type I carbohydrate specific soluble substance\* were added to the twice-washed pneumococcus Type I suspension. The blood samples containing horse serum and the pneumococci containing carbohydrate solution were then mixed and phagocytosis tests were run. Marked inhibition of the phagocytosis-promoting action of the therapeutic serum was obtained with all dilutions of soluble substance of 1 to 216,000 or less.

*Development of Antibodies Following Infection or Inoculation.* In the course of studies on the effect of pneumothorax on experimental pneumonia in dogs,<sup>16</sup> virulent Type I pneumococci have been injected in dogs intrabronchially by Dr. Louis Lieberman. The development of phagocytosis-promoting antibodies in a dog so infected is shown in Fig. 2, *D*. One-cc. portions of the dogs' blood were mixed with 600 million twice-washed Type I pneumococci and phagocytosis tests were run. The numerals in Fig. 2, *D*, indicate the days after infection on which the blood samples were taken for test; sample O was taken just before infection. It is evident that no detectable antibody response occurred for 5 days after infection. No test was made on the sixth day. The seventh day, phagocytosis-promoting antibody was detected and was prominent on the succeeding days.

The dog sera studied for phagocytosis-promoting power were tested also for agglutination and mouse protection. The results of the three tests were in general parallel. The phagocytosis test proved, however, to be distinctly more delicate than agglutination, and in a majority of instances also more delicate than mouse protection; in several cases the appearance of antibodies was detected a day or more earlier by phagocytosis than by the other tests.

*Phagocytosis by Cells Other Than Normal Neutrophils.* The technique of studying phagocytosis in whole blood affords an opportunity to compare under identical conditions phagocytosis by normal neutrophils with phagocytosis by any other cells which may appear in the blood in sufficient numbers. For instance, in looking over many slides the impression has been gained from the occasional eosinophil encountered that these cells were phagocytic but less actively so than the neutrophils.

An opportunity to check this observation was afforded by a patient with eosinophilia of unknown origin. The total count was 12,200 leukocytes per c.mm., of which 5612 were neutrophils (46%), 4148 lymphocytes (34%), 488 monocytes (4%) and 1952 eosinophils (16%). One-cc. portions of this patient's blood were added

\* For this we are indebted to Dr. Walther Goebel, of the Rockefeller Institute.  
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to 600 million smooth Type I pneumococci and to a heavy suspension of *Staphylococcus aureus*; also a portion of the blood containing 1 to 75 antipneumococcus horse serum was added to 600 million Type I S pneumococci. Phagocytosis tests were run and the rate curves for phagocytosis by neutrophils and eosinophils were separately determined (Fig. 2, E). It is evident that phagocytosis of pneumococci by neutrophils definitely exceeded that by eosinophils both with and without serum. With the staphylococcus this superiority of the neutrophils was not so apparent from the graph. Another method of analysis shown in Table 2 does bring out this superiority of neutrophils, however, with respect to ingestion of staphylococci as well as of pneumococci.

TABLE 2.—PHAGOCYTOSIS BY EOSINOPHILS AS COMPARED WITH NEUTROPHILS.  
1 Cc. of Blood Plus *Pneumococcus Type I S*.

Number of bacteria per cell.	Time in minutes.				
	3.	6.	9.	12.	15.
Eosinophils (100 observed):					
Over 10 . . . . .	0	0	0	0	0
5 to 10 . . . . .	0	0	0	0	0
1 to 5 . . . . .	1	6	3	8	4
Neutrophils (100 observed):					
Over 10 . . . . .	1	1	0	1	0
5 to 10 . . . . .	2	1	0	0	1
1 to 5 . . . . .	18	13	18	12	26

1 Cc. of Blood Plus Antipneumococcus Serum (1 to 75) Plus *Pneumococcus Type I S*.

Eosinophils (100 observed):					
Over 10 . . . . .	6	8	11	17	10
5 to 10 . . . . .	10	12	11	16	18
1 to 5 . . . . .	28	35	29	31	36
Neutrophils (100 observed):					
Over 10 . . . . .	30	65	90	93	88
5 to 10 . . . . .	20	19	5	5	4
1 to 5 . . . . .	20	15	3	2	8

1 Cc. of Blood Plus *Staphylococcus Aureus*.

Eosinophils (100 observed):					
Over 10 . . . . .	23	68	68	72	80
5 to 10 . . . . .	36	16	15	13	10
1 to 5 . . . . .	35	12	13	12	10
Neutrophils (100 observed):					
Over 10 . . . . .	66	100	99	100	100
5 to 10 . . . . .	28	0	0	0	0
1 to 5 . . . . .	6	0	1	0	0

*Type Specific Phagocytosis-promoting Antibodies in Human Blood.* The opsonization of human erythrocytes by human sera of incompatible types was demonstrated, in 1925, by Schiff.<sup>17</sup> This "iso-hemotropin" effect was found in only a certain proportion of human bloods; it occurred in association with isohemolysis and with isohemagglutination of relatively high titer.

We have confirmed these findings of Schiff, using first whole blood and later plasma-leukocyte mixtures prepared as outlined above. A representative result is given in Table 3. Fifty million erythro-

cytes of each type were added to plasma-leukocyte mixtures as indicated. The results of isohemolysis tests and the isoagglutination titers are given in the last columns of the table. The percentage phagocytosis at the several time intervals includes leukocytes containing stainable erythrocytes (*E*) and those containing only vacuoles of the size and shape of erythrocytes (*V*).

These vacuoles were interpreted as stromata of hemolyzed erythrocytes. This interpretation was confirmed by direct observation of the process of phagocytosis in film preparations<sup>18</sup> in a warm box, using a Zeiss cardioid dark-field condensor. Erythrocytes and hemolyzed stromata ("ghosts") can thus readily be distinguished. Using Type A erythrocytes sensitized with a Type O plasma which contained isohemolysin, the ingestion both of unlyzed erythrocytes and of ghosts was observed. Many of the ingested erythrocytes were hemolyzed intracellularly, and digestion and disappearance of the red cells and stromata regularly followed ingestion.

It will be observed that in Table 3, and this is representative of other similar data we have obtained, Type O plasma caused phagocytosis of Types A, B and AB cells, Type A plasma of B and AB but not of O cells, and that Type AB plasma caused no phagocytosis. This is in accord with expectation from the known distribution of isoantigens and antibodies. Type B plasma did not cause phagocytosis or hemolysis and was exceedingly weak in isoagglutination. This failure to promote phagocytosis or hemolysis we have found in the several B plasmas tested, but we have not yet analyzed the matter further.

Fig. 2, *F*, shows graphically the result of an experiment with O plasma and A erythrocytes. This plasma was hemolytic. The dotted line indicates the percentage of leukocytes containing stainable red cells and the broken line the percentage containing vacuoles. The solid line is the total percentage phagocytosis, *i. e.*, the sum of the percentages of stainable cells and vacuoles. The percentage of leukocytes containing unhemolyzed erythrocytes reached a maximum in 3 minutes, the percentage containing vacuoles, as would be expected, attained its maximum later, *i. e.*, at 10 minutes. After 10 minutes the rate of digestion and disappearance evidently surpassed the rate of ingestion of new elements, and the percentage phagocytosis thus appeared to fall. A similar effect due to intracellular digestion of typhoid bacilli has previously been described.<sup>19</sup>

*Reliability of the Method.* Current methods of estimating opsonic and phagocytic indices lose greatly in value through such sources of error as imperfect mixing, the use of anticoagulants which combine with calcium, and dependence on a single serum concentration and a single time of contact between phagocytes and test objects. We have sought to develop a method of direct estimate of phagocytic power, free from these errors, and suitable both for experimental and clinical use.

TABLE 3.—PHAGOCYTOSIS BY PLASMA-LEUKOCYTE MIXTURES OF ERYTHROCYTES OF INCOMPATIBLE TYPE.

Plasma, 0.5 cc.	Red cells, 50 million.	Leukocytes in millions.	1 min.		3 min.		5 min.		10 min.*		15 min.		Plasma- leukocyte hemolysis.	Serum* hemolysis.	Agglutination† complete.
			E.	V.	E.	V.	E.	V.	E.	V.	E.	V.			
O	A	12.5	44	12	80	10	86	10	70	14	88	6	Positive	Positive	1-32
O	B	12.5	40	5	71	12	80	8	70	19	73	22	Positive	Positive	1-64
O	AB	12.5	30	8	91	7	90	8	93	7	91	7	Positive	Positive	1-64
A	O	10.2	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
A	B	10.2	45	9	48	15	25	31	31	34	30	35	Positive	Positive	1-64
A	AB	10.2	20	12	34	13	34	13	29	26	29	21	Positive	Positive	1-32
B	O	28.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
B	A	28.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	1-4
B	AB	28.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
AB	A	9.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
AB	B	9.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
AB	O	9.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.

\* Serum hemolysis slower and not as complete as the plasma-leukocyte hemolysis.

† Lowest dilution, 1 to 2.

TABLE 4.—DESCRIPTIVE STATISTICS FOR PHAGOCYTOSIS OF TYPE I PNEUMOCOCCUS BY NORMAL DOG BLOOD, BLOOD OF ACTIVELY IMMUNE DOGS AND NORMAL DOG BLOOD PLUS IMMUNE HORSE SERUM.

Minutes of contact between blood and bacterin.																																
Group.	3.						6.						9.						12.						15.							
	N.		M.		σ		C.V.		N.		M.		σ		C.V.		N.		M.		σ		C.V.		N.		M.		σ		C.V.	
	I	51	2.45	2.99	122	52	3.71	3.80	102	51	4.84	4.59	94	52	5.94	5.35	91	55	6.08	7.00	115											
	II	23	35.35	20.52	58	23	49.01	27.45	59	23	62.39	27.43	44	23	60.48	27.46	41	25	61.92	27.93	45											
	III	15	35.40	20.48	83	15	68.47	25.38	37	15	81.20	10.03	20	15	80.07	15.32	17	14	87.79	12.43	14											

N = Number of observations.

σ = Standard deviation of observations from the mean.

M =

Arithmetic mean of per cent of cells showing phagocytosis in each observation.

C.V. = Coefficient of variation.

There remains for consideration the question as to what degree of precision and reliability may be expected of the method described. A general answer is not possible, since the reproducibility of the results depends upon factors peculiar to each system under consideration. However, in following the phagocytosis of virulent Type I pneumococci by the blood of dogs with experimental pneumonia, as described above, sufficient data have been obtained to permit of analysis by ordinary statistical methods (Tables 4 and 5).\*

TABLE 5.—COMPARISON OF PHAGOCYTOSIS BY DOG BLOOD IN GROUPS GIVEN IN TABLE 1, AND PROBABILITIES, *P*, OF DIFFERENCES BEING DUE TO ERRORS OF RANDOM SAMPLING.

	Groups.	Minutes of contact between blood and bacteria.									
		3.		6.		9.		12.		15.	
		<i>d.</i>	<i>P.</i>	<i>d.</i>	<i>P.</i>	<i>d.</i>	<i>P.</i>	<i>d.</i>	<i>P.</i>	<i>d.</i>	<i>P.</i>
Immune dog blood compared with normal dog blood	II-I	7.65	0	7.89	0	10.00	0	10.48	0	9.86	0
Normal dog blood plus immune horse serum, compared with normal dog blood	III-I	4.32	<.001	9.85	0	17.28	0	20.04	0	23.67	0

$$\text{Relative deviate} = d = \frac{M_2 - M_1}{\sqrt{\frac{\sigma_2^2}{N_2} + \frac{\sigma_1^2}{N_1}}}$$

The phagocytosis determinations are considered in three groups: Group I includes all determinations up to and including 96 hours after intrabronchial infection. Since no antibody response was detected up to this time, all these determinations are classed as upon "normal" dog blood. Group II includes all determinations upon dogs during the period when humoral immunity was well established, that is, from the eighth to the fourteenth day of infection, inclusive. Group III includes determinations upon dog blood, not of itself possessing immune antibodies, but with antipneumococcus horse serum added in a final dilution of 1 to 50. The percentages of neutrophils containing ingested bacteria are given separately in Table 4 for each time interval. *N* is the number of determinations in each category, *M* the arithmetic mean and  $\sigma$  the

$$C.V. = 100 \frac{\sigma}{M} \%$$

As compared with measurements of the sort more commonly given statistical treatment, the scatter of our values, as reflected in the standard deviations, is found to be great. It may be said, however,

\* We are indebted to Dr. Louis Lieberman for permission to publish data on these dogs at this time.



that the system under consideration is a particularly sensitive one, subject to great influence in one direction by traces of phagocytosis-promoting substances in the serum, and in the other direction by the inhibiting action of traces of bacterial specific soluble substances (Fig. 2, *B, C, D*). The conditions, moreover, were only average laboratory working conditions; at least 4 different observers, for instance, were engaged in counting the phagocytes, and individual differences in interpretation are unfortunately by no means impossible.

The coefficient of variation is seen to decrease in each group as the time of contact between blood and bacteria increases from 3 and 6 minutes to 12 and 15 minutes. This substantiates the impression of the workers that errors in time of sampling were relatively great at the shorter time intervals. With a test object which was not altered within the phagocyte, greater reliability was, therefore, obtained at the longer intervals. When intracellular digestion occurs, however, as with erythrocytes (Fig. 2, *F*), typhoid bacilli<sup>5</sup> and certain other cells, observations at a longer time interval alone may be very misleading.

In Table 5 the significance of the differences between the several groups are examined for statistical significance. The relative deviate,  $d$ , is determined from the formula,

$$d_{1,2} = \frac{M_2 - M_1}{\sqrt{\frac{\sigma_2^2}{N_2} + \frac{\sigma_1^2}{N_1}}}$$

The probability,  $P$ , that any given deviate may be due to errors of random sampling rather than to real differences inherent in the groups may be obtained from a suitable table of probability integrals.<sup>21,22</sup> In the present data, values of  $P$  are infinitesimally small in all cases, even in that of the deviate between Groups III and I at the 3-minute interval, in which case there are about 8 chances in a million that the difference observed might be due to sampling error.

The method of determining phagocytosis described, therefore, shows differences between these samples of normal dog blood, blood of actively immune dogs and normal dog blood plus immune horse serum which more than adequately satisfy the criteria for statistical significance.

**Summary.** A method for direct determination of the phagocytic power of whole blood or plasma-leukocyte mixtures, human or animal, is described. The following features are designed to eliminate sources of error in current methods: (a) Replacement by heparin of anticoagulants which combine with calcium. (b) A technique for collecting leukocytes from small samples of blood with a minimum of mechanical or chemical manipulation. (c) Provision of an agitator to provide continuous mixing of phagocytes and test

objects. (d) Determination of percentage phagocytosis as a function of time.

Examples are given of the application of this method to a variety of problems, *e. g.*, titration of the phagocytosis-promoting action of therapeutic serum, detection of antibodies following infection or vaccination, the relative resistance to phagocytosis of different bacterial strains and inhibition of phagocytosis by soluble bacterial products.

The blood of a patient with eosinophilia examined by this method showed phagocytosis by eosinophils, which was, however, quantitatively inferior to that by neutrophils in the same blood.

The opsonization of human erythrocytes by human sera of incompatible types, described by Schiff, has been confirmed. Intracellular lysis and digestion of ingested erythrocytes has been observed.

The reliability and significance of results obtained with the blood of dogs during the course of experimental pneumococcus infections are examined statistically.

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## EFFECT OF TISSUE EXTRACTS ON MUSCLE PAINS OF ISCHEMIC ORIGIN (INTERMITTENT CLAUDICATION).\*

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INTEREST in the therapeutic use of various tissue extracts for circulatory diseases originated from the work of Frey and Kraut, in 1926, who isolated a substance from urine which lowered blood pressure when injected intravenously into animals. This substance was subsequently named kallikrein (later padutin) and was found by Frey<sup>1</sup> to inhibit the pain of angina pectoris and intermittent claudication, and to lower blood pressure in cases of hypertension when administered intramuscularly to human beings. Later Frey<sup>2</sup> found that the fluid from a pancreatic cyst had similar properties, and concluded that the effects of kallikrein were attributable to a hormone present in many tissues but elaborated in the pancreas. Gley and Kisthinios, and later Wolffe, Findlay and Dessen, described extracts of pancreatic tissue which gave therapeutically similar results. J. S. Schwarzmenn prepared an extract of skeletal muscle, which he called myoston, and reported improvement in cases of angina pectoris after injecting it intramuscularly. M. S. Schwarzmenn noted marked improvement in 3 cases of intermittent claudication after treatment with myoston. In small series of cases in which there was occlusive disease of the arteries of the leg and intermittent claudication, pancreatic tissue extract has been reported to have increased the walking distance, but controlled tests before medication was used were not mentioned. This effect on tolerance to exercise has been considered to be the result of vasodilatation. Experimental work in animals has shown that pancreatic extract and kallikrein produce a transient fall in blood pressure when injected intravenously, and cause dilatation of the coronary arteries when perfused into a rabbit's heart;<sup>3</sup> however, when perfused

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through the arteries of the leg of a rabbit, Nuzum and Elliot noted vasoconstriction. Topical applications of pancreatic tissue extract cause vasodilatation in the frog's foot and inhibit the effect of epinephrin on dogs when injected intravenously.<sup>11</sup> The physiologic properties have been felt to be distinct from histamin and cholin<sup>11</sup> and from adenosin.<sup>3</sup>

It is noteworthy, however, that both the pancreatic tissue extract and myoston are undoubtedly mixtures of various organic compounds, and that when used therapeutically they have been injected intramuscularly, and not intravenously or by perfusion. Nuzum and Elliot were unable to demonstrate vasodilatation in animals after intramuscular or subcutaneous injections of kallikrein. Actual evidence is lacking that the therapeutic effects observed in cases of intermittent claudication are due to vasodilatation.

Intermittent claudication is one of the most constant and significant symptoms seen in medical practice. It results from the occlusion of the larger arteries of the extremities, due either to thromboangiitis obliterans or to arteriosclerosis obliterans in 90% of our cases. Patients describe intermittent claudication as a pain, ache, cramp or sense of extreme fatigue localized in certain muscle groups and induced by a certain amount of muscular exercise. If the exercise is continued, muscular spasticity and weakness, and sometimes true cramp, are added to the pain. This pain or sense of fatigue is never present during rest, and it is relieved in a few minutes by cessation of the muscular effort without change in posture. The amount of muscular effort necessary to produce intermittent claudication is remarkably constant during any one phase of the individual's disease.

We have studied the effects of pancreatic tissue extract, of two types of skeletal muscle extract and of adenosin, on intermittent claudication. The cutaneous temperature of the digits was measured in a room of controlled temperature, to determine whether significant vasodilatation occurred.

In order to evaluate the effect of the various tissue extracts, it was necessary to have a standardized test for claudication. Our test is as follows: After a rest of one-half hour, the patient walks on a level floor, with one of us as a pacemaker, at the rate of 120 steps per minute, until sufficient distress occurs to cause him to stop. The time elapsed from the beginning of the walk until cessation of it is designated as the "claudication time." Although this involves a factor of subjective sensation in determining the end point, objective evidence, such as limping, muscular weakness or spasticity usually precedes this end point. Sixteen patients with occlusive arterial disease were tested repeatedly on various days in the same environmental temperature and have shown an average variation of only 10% from their shortest claudication time. The maximal variation was 20%. The claudication time

was determined and frequently was verified 2 or 3 times before the extracts were given. The extract was then injected into the triceps muscle of the arm; hot, moist towels were applied and the muscle was gently massaged.

**Pancreatic Tissue Extract.** The first extract studied was the insulin-free pancreatic tissue extracts,\* which Wolffe previously had described and standardized by means of its power to neutralize epinephrin. The dose was arbitrarily fixed at 3 cc., as this seemed to give the maximal effect in the majority of cases; however, in a few instances a greater effect was noted after injection of 4 or 5 cc. Some variation was noted in the potency of the various lots of this extract.

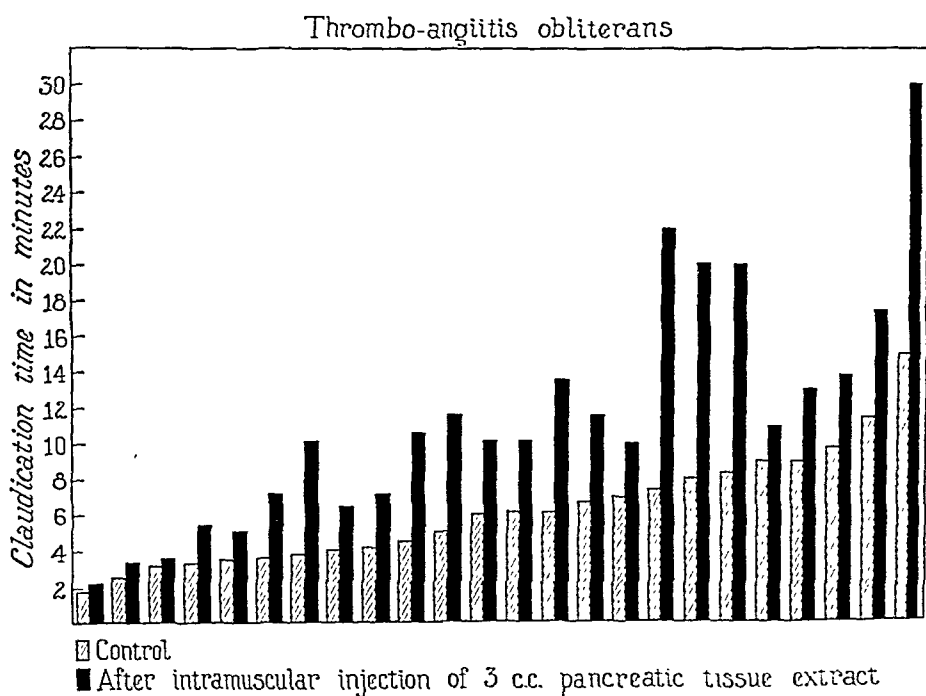


FIG. 1.—Effect of pancreatic tissue extract on intermittent claudication in twenty-four cases of thromboangiitis obliterans.

We have previously reported<sup>2,8</sup> the effect of this extract on 22 patients with definite occlusive arterial disease of the legs. Since that time we have tested 33 additional patients (Figs. 1 and 2). In the entire series of 55 cases, the diagnosis of arteriosclerosis obliterans had been established definitely in 20 cases, and thromboangiitis obliterans in 35 cases; all of the patients had typical intermittent claudication. The results for the entire series have been similar to those noted in the original 22 cases. Definite lengthening of claudication time was noted in 50 (92%) cases, and the average

\* Tissue extract No. 56S, Sharp & Dohme.

claudication time for the entire group was increased 1.85 times. The average results were slightly better in the group of cases of thromboangiitis obliterans than in the group of cases of arteriosclerosis; in the former, the increase, as compared with the control test, was 1.98 times, and in the latter, 1.65 times. In 6 cases no claudication was produced after 20 minutes of standard walking. The poorest results were noted in cases in which the control claudication time was short and in which marked degrees of arterial insufficiency of the legs were present. Generally, definite improvement was noted  $1\frac{1}{2}$  to 2 hours after the injection, but the maximal improvement usually occurred after 24 hours. The increased claudication time was maintained for from 2 to 7 days, usually 4 days, after which there was gradual return to the original claudication time.

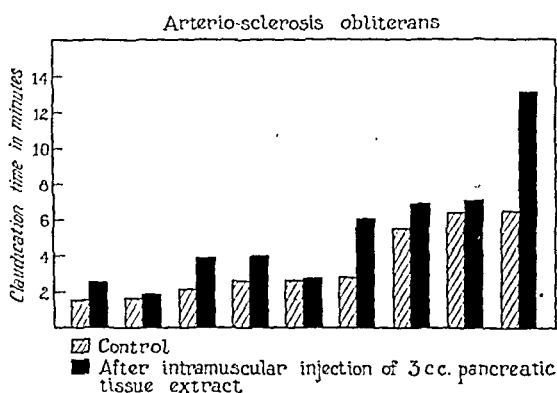


FIG. 2.—Effect of pancreatic tissue extract on intermittent claudication in 9 cases of arteriosclerosis obliterans.

**Extract of Skeletal Muscle (Myoston).\*** The skeletal muscle extract was prepared according to the method of J. S. Schwarzmänn, and it was standardized on the basis of its content of adenosin phosphoric acid, 1 cc. containing 2.5 mg. Myoston was given intramuscularly, by the same technique as that employed in giving the pancreatic extract, to 13 patients, 5 of whom had arteriosclerosis obliterans and 8 thromboangiitis obliterans. All of them had constant, intermittent claudication. The results which are given in Fig. 3 were similar in effect and in duration of effect to those following use of the pancreatic extract in the cases of thromboangiitis obliterans. In all, there was definite lengthening of the claudication time; the average was 2.1 times the control average. However, in only 1 of the 5 cases of arteriosclerosis was any marked improvement noted.

Myoston was administered orally in amounts of from 5.3 to 16 cc., over periods of from 1 to 3 days, to 8 patients; 2 with arteriosclerosis

\* Myoston: Dr. George Henning (Chem. u. pharm. Fabrik), Berlin.



**Muscle Adenosin Phosphoric Acid.** More recently we have studied the effects of another muscle extract, muscle adenosin phosphoric acid (M.A.P.), obtained from the same source as myoston. This extract was administered intramuscularly in doses of 20 mg. in a 1% solution to 4 patients, 2 with arteriosclerosis obliterans and 2 with thromboangiitis obliterans; all of the patients had intermittent claudication. The effects are shown in Fig. 5. Definite lengthening of claudication time was noted in all the cases, but the average was only 1.6 times the control claudication time.

**Adenosin.** It has been suggested that adenosin or adenosin phosphoric acid was the active portion of all of these extracts.

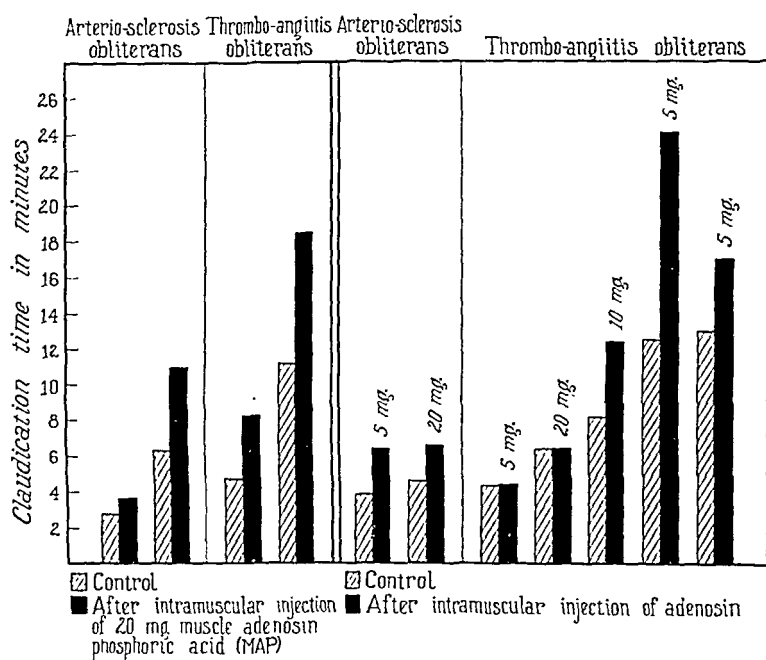


FIG. 5.—Effect of muscle adenosin phosphoric acid and adenosin on intermittent claudication in arteriosclerosis obliterans and thromboangiitis obliterans.

We tested the effect of pure adenosin given intramuscularly in physiologic solution of sodium chlorid, in amounts of from 5 to 20 mg. It was given to 7 patients, 2 with arteriosclerosis obliterans and 5 with thromboangiitis obliterans (Fig. 5). In 2 cases of the latter group lengthening of the claudication time did not appear. The average increase was 1.4 times that of the control claudication time. Thus, the average results with adenosin and muscle adenosin phosphoric acid were slightly inferior to those with pancreatic tissue extract, which has a very small content of adenosin phosphoric acid.

None of the patients tested with any of the extracts had untoward effects. There was usually moderate pain of short duration at the



site of the injection, but there were no chills, fever or evidences of histamin-like or foreign protein reactions.

**Effects on Surface Temperature.** The effect of pancreatic tissue extract on the cutaneous temperature of the toes, as a measure of vasodilatation, has been negligible in our experience. In 3 cases, temperatures of the skin were observed for 24 hours, immediately before and immediately after administration of 3 cc. of the extract. The curves were practically identical. In 12 other cases, in which the cutaneous temperatures were observed, during a control period, and for at least 2 hours after administration of the extract, the maximal rise was  $2.9^{\circ}\text{C}$ ., and this lasted only 1 hour; the average rise was  $0.8^{\circ}\text{C}$ . In 3 cases, in which similar tests were made after intramuscular administration of myoston, the maximal rise was  $1.6^{\circ}\text{C}$ . and the average  $0.3^{\circ}\text{C}$ . In 2 of 3 cases, following administration of muscle adenosin phosphoric acid, there was definite vasodilatation, shown by a transient rise of  $3.2^{\circ}\text{C}$ . This may have been due to the greater content of adenosin, for in 3 cases in which pure adenosin was given the rise in temperature was  $4.6^{\circ}$  to  $8.2^{\circ}\text{C}$ . This vasodilatation lasted only 1 to 2 hours, and on the following day, when the cutaneous temperatures had returned to their basic levels, the claudication time was most greatly increased. In 4 cases in which repeated tests were made, both as to claudication time and cutaneous temperatures, each of the patients received several, or all, of the different extracts, with definite increase in claudication time. There was absolutely no correlation between claudication time and the cutaneous temperatures.

It has been our experience that definite vasodilatation does not significantly affect intermittent claudication. In 2 cases in which tests were made before and during artificially induced fever there was no increase in claudication time. In both of these cases there was definite increase with the extracts. Even after extensive intravenous treatment with typhoid vaccine, little effect has been noted on intermittent claudication.<sup>1</sup> In 1 case increase in claudication time was not noted either after 20 gr. (1.3 gm.) of theobromin, given orally, or later, after 0.2 gm. of theophyllin ethylenediamin, given intravenously, both of which produced definite vasodilatation. However, a 200% increase in claudication time was then noted after 16 cc. of myoston had been given by mouth over a period of 2 days. In 1 case, no difference in claudication time was noted during tests before, and 4 weeks after, lumbar sympathetic ganglionectomy, which caused a sharp increase in surface temperature, but there was a 100% increase after 3 cc. of pancreatic tissue extract had been given intramuscularly.

**Comment.** We feel that results of this study have confirmed, by actual measurement of work done, the opinions of certain previous investigators that pancreatic tissue extract and myoston, given intramuscularly, do inhibit or delay intermittent claudication in

the great majority of cases in which it occurs. The exact component of the extracts responsible for the effect is not known, but must be common to both the pancreas and skeletal muscle. In the present state of knowledge, the method of action also seems obscure. It has been our experience that the extracts have little or no effect on the pretrophic pain, or on the pain which results from the ulceration and gangrene which occurs in occlusive arterial disease. This seems to exclude analgesia. We cannot concur with the beliefs of previous investigators that in intermittent claudication the therapeutic effect of these tissue extracts, when given intramuscularly, is the result of vasodilatation. We have not demonstrated that definite index of the vasodilatation, namely, significant rise in cutaneous temperature, and the effects on claudication far exceed those observed after definite vasodilatation produced by drugs, sympathectomy or artificially induced fever. It seems probable to us that the therapeutic effect consists in supplying some substance to the actively contracting muscle which it cannot obtain in sufficient concentration, with a restricted supply of arterial blood. The evidence is not conclusive that adenosin phosphoric acid is the active substance, but it may have a similar action. Further studies are being carried out on this phase of the problem.

From the practical standpoint, the therapeutic value of the tissue extracts in peripheral arterial disease seems to us to be restricted to those cases in which intermittent claudication is the chief symptom and trophic lesions are not present. Individual testing is advisable in all cases, to note the extract and dosage that will give the optimal effect. Most patients seem to do satisfactorily on one injection a week. We have noted, in a number of cases, that after a series of 8 to 16 weekly injections of one of the extracts the improvement was maintained for several months. If myoston is administered by mouth it is necessary to give it at least on alternate days in fairly large doses, and the cost of a sufficient amount to maintain the effect over periods of time is almost prohibitive at present.

**Summary.** Definite lengthening of the time necessary to produce intermittent claudication during a standard claudication test was noted in 92% of a series of 55 cases of thromboangiitis obliterans and arteriosclerosis obliterans, following intramuscular injections of pancreatic tissue extract. Similar effects were noted in all of a series of 8 cases of thromboangiitis obliterans after intramuscular administration of myoston, a skeletal muscle extract. In only 1 of 5 patients with arteriosclerosis obliterans was an increase in claudication time noted after myoston had been given intramuscularly. In 75 per cent of a series of 8 cases of intermittent claudication, in which the patients received myoston orally, an approximately equal, but more transient, effect was noted. Definite, but less striking increases in claudication time were noted in 4 cases in

which patients received muscle adenosin phosphoric acid (M.A.P.) intramuscularly and in 4 cases in which patients received adenosin intramuscularly.

Evidence is presented to show that these effects are not the result of vasodilatation but are the result of some direct action on the contracting ischemic muscles.

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### A STUDY OF THE SPUTUM IN PULMONARY ASBESTOSIS.

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So much has been written on pulmonary asbestosis during the few years which have elapsed since its first recognition (Cooke, 1924, 1927; Stuart McDonald, 1927; Merewether, 1930; Lynch and Smith, 1930; Kruger *et al.*, 1931; Ellman, 1933) that only a brief introductory statement is necessary here. The disease is a slowly progressive fibrosis of the lungs due to the inhalation of asbestos dust. The fibrosis is widespread, mainly basal and sub-pleural in distribution, and leads ultimately to such extensive destruction of the parenchyma that the most serious functional disability results. Death is usually brought about by some inter-current infection, tuberculosis, influenza, or some form of pneumonia. The length of exposure to dust has varied within wide limits, but it is clear that gross disease may follow even as short an exposure as 18 months, provided the dust concentration has been sufficiently high. A certain interval of time must elapse before the disease seriously manifests itself, possibly a period of 7 years (Merewether, 1933-1934). At a certain stage of its development the disease can be diagnosed with great assurance on clinical and radiological

examination, the more so as a clear industrial history of exposure to asbestos dust is almost invariably available. In the earlier stages of disordered function it may be possible only to suspect that a lesion is developing.

**The Asbestos Body.** This has attracted much attention since it was first adequately described and its probable significance pointed out by Stuart McDonald (1927). A detailed description is given by Gloyne (1932). The bodies are formed in the lung aveoli by the deposition around individual asbestos fibers of an iron-containing silica gel, derived partly from the fiber, partly from the surrounding fluids. They are highly characteristic in form, while presenting considerable individual variation. The two chief varieties are: (1) a spindle-shaped elongated form, very slender in the center and swelling gradually to bulbous extremities, and (2) a beaded form, with the smallest elements in the center and a gradual increase in size to large terminal knobs. In the latter form, the central core of asbestos fiber can often be made out very clearly, especially if the body has been fractured, as often happens. The bodies, which range in size from a few up to several hundred microns, vary in color from pale green through golden yellow to deep brown, depending mainly on their size. They give the Prussian blue reaction with corresponding grades of intensity.

The bodies were first observed in sections of the lung, where they occur singly, in small groups and in radiating clumps in the alveoli, or embedded in the fibrous tissue of the grossly diseased areas. They were next recovered from lung juice obtained by exploratory puncture of the chest during life (Stewart and Haddow, 1929) and finally these observers were able to demonstrate their presence in the sputum of asbestos workers. Later Stewart, Tattersall and Haddow (1932) recovered clumps of bodies similar to those seen in the lung alveoli postmortem from 2 cases of asbestosis, one advanced and since dead of the disease, the other moderately advanced. They suggested that the presence of such clumps meant disintegration of lung tissue and was of much greater significance than the finding of individual bodies, which merely indicated that there had been exposure to asbestos dust.

**Personal Observations.** The following observations are based partly on Professor Stewart's collected material, partly on a reinvestigation of the cases which he had previously examined, and partly on a few new cases first seen during the first half of 1934. Thirty-eight individual cases have been studied, and a large number of specimens of sputum examined.

Of these cases 11 have died and in 10 the presence of asbestosis was confirmed postmortem. In 6 cases there was superimposed pulmonary tuberculosis, in 2 a terminal acute bronchitis and in 1 the proximate cause of death was influenza. In 1 case death followed pregnancy and parturition and in 1 (Case 14) an abdominal

operation. In this case no autopsy was obtained. Of the surviving cases, 2 are now acutely ill with pulmonary tuberculosis, 2 are doubtfully tuberculous, while 9 are apparently uncomplicated cases of pulmonary asbestosis of considerable and progressive severity. Four others present evidence of mild asbestosis. Adequate information is lacking in regard to 7 of the remaining 10 cases, while the other 3 are in excellent health. Of these, 2 are office employees and the third was employed in an asbestos factory only after the introduction of modern methods. In consequence she was exposed to a minimum amount of dust.

Detailed examination of these cases has been going on at varying intervals for a period of 5 years. Several have been receiving medical attention for indefinite periods and the sputum has been examined at intervals when conditions permitted. Patients with pulmonary asbestosis are extremely susceptible to chest colds and coughs, particularly so during the damp winter months. It is upon such occasions that the ever-present cough becomes productive and that sputum may be obtained for examination.

The best time to obtain a specimen is in the morning owing to the accumulation of mucus overnight. The type of sputum varies: usually in an uncomplicated case it is very thick and tenacious and when allowed to stand develops a very disagreeable odor. When tuberculosis is associated, pus and streaks of blood are not infrequently present. The consistency in many cases is not uniform; clear, thin, watery mucus, when present, tends to settle out from the underlying thick and stringlike portion.

In conjunction with this work complete clinical and radiologic examinations have been done wherever possible. In the developed disease dyspnea and cough are the ever-present and progressive symptoms. Physical signs are for the most part localized to the region of the lower chest. Roentgen ray examinations invariably confirm the findings on physical examination, and when taken at infrequent intervals illustrate a definite bilateral progressive, mainly basal, fibrosis, with characteristic signs of old pleurisy, hazy diaphragmatic margins, and so on. Complications in the nature of upper respiratory infections, bronchitis, bronchiectasis, empyema, pneumonia and especially tuberculosis, aggravate the symptoms to a notable degree, with greatly increased debilitation of the patient and evidence of right heart failure. In all cases the sputum has been examined for the presence of asbestos bodies (including clumps) and tubercle bacilli, and in a small group of 6 cases a special search for elastic tissue has been made.

**Technique for Demonstration of Asbestos Bodies.** The method originally suggested by Stewart and Haddow (Stewart, 1929) consisted in adding to selected portions of the sputum an equal quantity of antiformin. Following gentle agitation in a test tube and the addition of 4 or 5 times the volume of water, the mixture is placed in the incubator at 37° C. for some hours.

The supernatant fluid is now poured off and the last 10 to 15 cc. centrifuged for 5 or 10 minutes. The supernatant fluid is again poured off and the precipitate, by means of a very fine pipette, is placed on albuminized slides. The films are dried, fixed and washed, and mounted in Canada balsam.

Simson and Strachan (1931) suggested a direct method. Thick films of the mucoid portion of sputum were made and dried in a paraffin oven at 54° C. These were fixed with saturated mercuric chlorid solution and subsequently stained with hematoxylin and eosin. These workers concluded that "it was as easy to demonstrate bodies in the direct film as in the anti-formin method" and recommended its use as showing both the cytology of the specimens and the intracellular development of the asbestos bodies.

Gloyne (1931) describes a method in which ammonium sulphate replaces the hematoxylin. After anti-formin digestion and centrifugation the anti-formin is pipetted off and replaced by 5% ammonium sulphid. The bodies as a result are colored black. The author recommends this method because it allows the minute details of the body to be clearly seen, while the central core of asbestos fiber can readily be observed extending between adjacent segments of the asbestos body.

Dr. Norah Schuster (Ellman, 1930-1931) uses the following simple wet method: The sputum is mixed with an equal quantity of 4% sodium hydroxid and left in the incubator until the mucus is dissolved (about 1 hour usually). Following centrifugation a wet film of the deposit is examined directly without staining.

The method used in the present study (Stewart, 1934) is substantially the same as the original.

**Technique for Demonstration of Elastic Tissue.** The sputum was prepared for staining by the method of Gentz and Bennet (1931). Three or 4 cc. of selected portions of sputum are placed in a centrifuge tube and 2 or 3 times this volume of 3% caustic potash is added. It is then shaken energetically until the mixture is homogeneous. Heat to the boiling point is now applied. Rapid cooling follows and the mixture is centrifuged for  $\frac{1}{2}$  to 1 minute. The supernatant fluid is poured off and the deposit placed on albuminized slides and allowed to dry. After being fixed with heat the films are carefully washed to remove the caustic potash.

Two methods of staining have been used for the demonstration of elastic fibers, one a modification of Barth's method (Calmette, 1928), the other a variant of Rappaport and Ellison's (1928-1929) modification of Weigert's stain. In Method I, Barth's orcein stain is heated to 55° C. and the slides immersed. They are kept at this temperature for from 1 to 2 hours, and are then washed in water, differentiated in acid alcohol (2 to 3% hydrochloric acid in 95% alcohol), washed again in water, dehydrated in absolute alcohol, cleared in xylol and mounted in Canada balsam. The elastic fibers are stained a dark reddish purple.

In Method II, the films are immersed in Weigert's stain, as prepared by Rappaport and Ellison, for a period of 20 minutes, following which they are washed in water, differentiated in acid alcohol (2 to 3% hydrochloric acid in 95% alcohol), washed again in water, dehydrated in absolute alcohol, cleared in xylol and mounted in balsam. Elastic fibers are stained a deep blue-black.

The relative merits of these two methods of staining are as follows: The stain as used in the Barth method is relatively easier to prepare, and once prepared can be used for an unlimited time, while the modified Weigert's stain, besides being far more difficult to prepare, tends to deteriorate much more quickly. On the other hand it stains elastic tissue in 20 minutes, whereas the modified Barth method takes from 1 to 2 hours. The final result is equally efficient and each can be used as best fitted to the individual laboratory.

TABLE 1.—LIST OF CASES.

Case No.	Sex and age (yrs.).	Duration of exposure to dust (yrs.); nature of work.	Interval since leaving employment (yrs.).	Interval since first exposure to dust (yrs.).	Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum.		
							Bodies.	Clumps.	Tubercle bacilli.
1	F 25	4 Mattress making	2	6	Always subject to catarrh; Roentgen ray negative for both tuberculosis and asbestosis. No definite Roentgen ray evidence of asbestosis. Now, 2 years later, apparently in excellent health. Very mild fibrosis; continuous dry hacking cough.	3 4	— —	— —	— —
2	M 34	3 Spinner	3	6	Excellent health; no cough.	2	+	—	—
3	M 36	7 Office worker	Still empl.	7	Excellent health; no cough.	2	+	—	—
4	M 28	10 Office worker	Still empl.	10	Excellent health; no cough. Now, 5 years later, still in excellent health.	5	+	—	—
5	F 27	10 Spinner	Still empl.	10	Cold; cough; gastritis; thought to be due to asbestos dust; definite jaundice. Pulmonary asbestosis.	5 10	— +	— —	— —
6	F 27	6 Teaser and corder	4	10	Definite progressive basal fibrosis.	9	+	—	—
7	M 30	9 Every dept.	4	10	Pulmonary tuberculosis superimposed on asbestosis. Confirmed postmortem 7 months later.	9½	++	+	+
8	M 45	13½ Associated with much dust	Still empl. clerk	13	Bilateral asbestosis with associated tuberculosis. Confirmed postmortem 1 year later.	12	++	+	—
9	M 37	12 White dust	3	15	Bilateral pulmonary asbestosis with suggested superadded tuberculous infiltration of upper zone of right lung.	14	++	+	—
10	M 46	11 Mattress maker	3	16	No data. Died of pulmonary asbestosis with superimposed tuberculosis 3 years later; confirmed postmortem.	12	++	—	—
11	F 31	15 Mattress maker	1	16	Advanced pulmonary asbestosis, bronchitis and cardiac failure; confirmed postmortem.	16	++	+	—
12	F 31	1 Mattress maker	16	17	Progressive pulmonary asbestosis of moderate severity. Similar state. Bronchitis.	15 16 17	+++ ++ +	— — —	— — —
13	F 44	15 Spinner	1	16	Emphysema with dyspnea, cough and pain in abdomen. Very ill; cirrhosis of liver(?). Later laparotomy was done; death followed.	12	+++	—	—
14	M 55	18 Foreman mattress maker	4	18	Pulmonary tuberculosis and asbestosis. Confirmed by postmortem 1 year later.	15 17	+++ ++	— —	— +
15	M 36	6 Spinner	12	18	Pulmonary asbestosis complicated by tuberculosis.	18	++	+	+
16	M 43	20 Spinner	..	..	(?) Tuberculosis plus asbestosis.	..	+	—	—
17	M (?)	18 Mattress maker	3	21	Progressive pulmonary asbestosis with cardiac involvement. Died 1 year later following pregnancy and parturition.	20+	+	—	—
18	F 35	6 Mattress maker	16	22	Right-sided basal pleural thickening; dyspnea, cough; tubercle suspected; tuberculosis confirmed. Primary pulmonary asbestosis with superimposed active tuberculosis.	20	+++	+	+
19	F 35	17 Mattress maker	2	22	Pulmonary asbestosis. Progressive pulmonary asbestosis.	22 19 22	+++ ++ ++	— — +	— — —
20	M 47	6 Mattress maker	15	23	Cerebral softening; acute bronchitis and bronchopneumonia with associated asbestosis. Confirmed later, postmortem.	23	+	+	—
21	F 45	19 Mattress maker	4	23	Cough, dyspnea; evidence of basal fibrosis by Roentgen ray examination. Death from acute influenza 2 years later.	21	+	—	—
22	F 41								

\* Elastic tissue present (Cases 5, 16, 20).

TABLE 1.—LIST OF CASES—Continued.

Case No.	Sex and age (yrs.).	Duration of exposure to dust (yrs.); nature of work.	Interval since leaving employment (yrs.).	Interval since first exposure to dust (yrs.).	Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum.		
							Bodies.	Clumps.	Tubercle bacilli.
23	F	22	2	24	Mild pulmonary fibrosis.	18	+	+	—
40	F	Mattress maker			Progressive pulmonary asbestosis.	24	+	—	—
24	F	4	14	24	Pulmonary asbestosis with tuberculosis.	23	++	—	+
37	F	Spinner			Asbestosis with extensive phthisis confirmed by postmortem 1 year later.				
25	F	16	9	25	Suggestion of pleural effusion.	22	+	—	—
44	F	Mattress maker			Progressive pulmonary asbestosis.	23	+	—	—
26	F	13	10	26	Two years later, advanced asbestosis, dry cough.	21	+	—	—
39	F	Mattress maker			Pulmonary asbestosis.				
27	F	21	2	29	Uncomplicated pulmonary asbestosis of pronounced severity.	26†	+	—	—
46	F	Mattress maker			Progressive pulmonary asbestosis.	27	++	+	—
28	M	30	Still empl.	30	Uncomplicated pulmonary asbestosis.	29†	++	+	—
63	M	Cashier			Very severe cough, dyspnea; mild pulmonary asbestosis.	25	++	—	—
29	M	35	Still empl.	35	Pulmonary asbestosis and tuberculosis confirmed later postmortem.	30	++	—	++
55	M	Warehouse man			General condition fairly good.	35	++	—	—
30	F	31	4	35	Fairly advanced fibrosis (Roentgen ray examination).	26	++	—	—
67	F	Mattress maker			Progressive uncomplicated pulmonary asbestosis.	31†	++	—	—
31	M	50	..	50	Advanced pulmonary fibrosis.	50	+++	—	—
63	M	Fiber rope dept.							

† Lung juice.

† Elastic tissue not present on repeated examinations (Cases 26, 27, 30).

**Analysis of Cases.** The present study includes 38 cases of asbestos workers of whom 31, where full details are available, are recorded in the preceding table. The cases have been arranged in accordance with the period of time that has passed since they first became exposed to asbestos dust, which in several cases is not equivalent to the actual duration of exposure plus the interval since leaving employment, since some were employed irregularly or were absent from work on account of childbirth, service overseas, etc.

Twenty-one of the cases are males and 17 females. The age at which they began working in an asbestos factory ranges from 13 to 39, average 21, but 17 of the 31 recorded in the table began work before the age of 21. The average duration of exposure is 15 years, with a range from as low as 1 up to 50 years. Tuberculosis was present in 8 cases, and in this group the average period of exposure was 9.2 years, as contrasted with 16 years in the non-tuberculous group. Case 28 is exceptional in that he was not really a worker in asbestos and he is therefore not included in the averages given.

**Sputum Examination.** *Asbestos bodies* have been present in every case with the exception of Case 1, a woman, aged 25, who was in contact with a minimum amount of dust as a mattress maker for



4 years, the whole period being subsequent to the abolition of the dry method of manufacture. She has always been subject to respiratory tract catarrh, which may have been a factor in preventing entry of dust to the lung alveoli. With two exceptions (Cases 1 and 5) bodies were demonstrated at every examination. In Case 5 the sputum was negative after 5 years' exposure but positive (a solitary body only) when examined after 10 years' exposure.

The number and type of bodies were most variable. Generally the large beaded or "weathered" type of bodies, deep brown in color and strongly iron-reacting, were most prevalent in cases where the interval since the onset of exposure had been long, including those where a long interval had elapsed since they were last employed in asbestos. Bodies recovered from those who had only been in this employment for a few years were smaller in size, paler in color and less strongly iron-reacting. It is clear that asbestos bodies in the lung slowly increase in size with the passage of time and become in consequence both darker in color and more strongly iron-reacting.

*Clumps or groups of bodies* were present in 10 of the cases. Five of these had tuberculosis, of whom 3 have died and the other 2 are critically ill. One of the remaining 5 cases is doubtfully tuberculous, 1 has died of pulmonary asbestosis with associated cardiac failure, while the remaining 3 are apparently cases of progressive uncomplicated asbestosis.

In 6 cases (Nos. 5, 16, 20, 26, 27 and 30) the sputum was examined for *elastic tissue* by the methods described and a positive result obtained in 3. In Case 5 a solitary "weather-beaten" asbestos body was discovered after 10 years' exposure, yet elastic tissue was present (Fig. 1). In Cases 26 and 30, bodies had been found on several former occasions but neither clumps nor tubercle bacilli; elastic tissue was absent from both. In Cases 20 and 27 clumps as well as single bodies had been found previously but no tubercle

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#### LEGENDS FOR FIGS. 1 TO 7.

FIG. 1.—Case 5, F., age 25. Elastic tissue in sputum of asbestos worker. Ten years' exposure to asbestos dust. Only one "weather-beaten" body found, no clumps, no tubercle bacilli.  $\times 300$ .

FIG. 2.—Case 20, M., age 47. Elastic tissue in sputum of asbestos worker. Twenty-two years since onset of exposure (duration 17 years). Asbestos bodies and clumps present, but no tubercle bacilli.  $\times 300$ .

FIG. 3.—Case 16, M., age 43. Elastic tissue in case of asbestosis with tuberculosis. Eighteen years since onset of exposure (duration 6 years). Elastic fibers, asbestos bodies and clumps (Fig. 7) and tubercle bacilli all present.  $\times 300$ .

FIG. 4.—Elastic tissue in sputum of a pure case of pulmonary tuberculosis.  $\times 300$ .

FIGS. 5 and 6.—Case 28, M., age 63. Elastic tissue in caseous material in a phthisical cavity. Case of pulmonary tuberculosis superimposed upon asbestosis. Interval since onset of exposure 30 years.  $\times 300$ .

FIG. 7.—Case 16. Small clump of asbestos bodies in sputum, from same case as Fig. 3.  $\times 300$ .



Fig.1



Fig.2

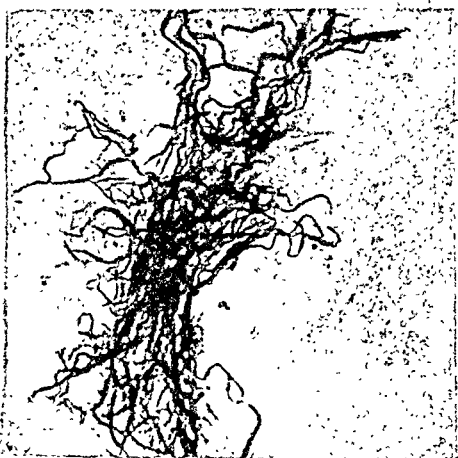


Fig.3

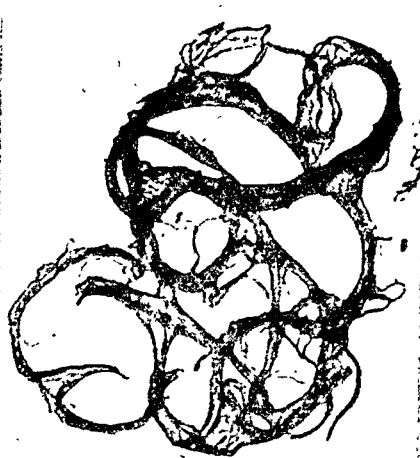


Fig.4



Fig.5



Fig.6

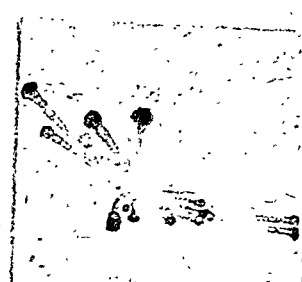


Fig.7

FIGS. 1 TO 7.

bacilli; elastic tissue was demonstrated in Case 20 (Fig. 2). In Case 16, clumps, tubercle bacilli and elastic tissue were all present (Figs. 3 and 7). These results are summarized in Table 2.

TABLE 2.—CASES EXAMINED FOR ELASTIC TISSUE.

Case No.	Asbestos bodies.	Clumps.	Elastic tissue.	Tubercle bacilli.
5 . . . .	+ (1)	—	+	—
16 . . . .	+	+	+	+
20 . . . .	+	+	+	—
26 . . . .	+	—	—	—
27 . . . .	+	+	—	—
30 . . . .	+	—	—	—

**Discussion.** The findings here reported are for the most part in accordance with those of other workers and show that the mere presence of asbestos bodies in the sputum of an individual denotes nothing more than that he has at some time been in contact with asbestos dust. The actual number of bodies is likewise of little significance. If, however, they are consistently present in considerable numbers the possibilities are that either the individual has been in contact with large quantities of dust over a long period or there is some underlying pathologic condition of the lung, leading to gradual liberation of accumulated bodies. This is illustrated in Cases 14 and 19. In the former the sputum upon repeated examination showed large numbers of bodies, the individual in question having been associated at the time of examination and for 15 years previously with large quantities of dust. Case 19, on the other hand, also with numerous bodies on repeated examination, had only been directly exposed for a period of 6 years and had not been in contact with dust for 16 years at the time of examination. Clinically there was an associated tuberculosis.

The type of body present is of considerably greater significance than the number. The formation of asbestos bodies in the lung takes but a short time. They were found by Simson (1929) in the lungs of a patient who had been exposed for 2 months only, and by Stewart (1930) in a guinea pig after 3 months' exposure in an asbestos factory. Once formed, they can remain in the lung for an indefinite period. In a patient of Ellman's (1933) exposure was for 10 weeks only, and 5 years later bodies were recovered from the sputum. In Case 13 of this series, the patient had worked in asbestos for 1 year, and 17 years later bodies were still present in small numbers.

Reference has already been made to the "growth" or increase in size of these bodies, presumably by slow diffusion out of silicates from the central fiber and their interaction with constituents of the surrounding body fluids. It follows that bodies of large size in the sputum indicate that these have formed around fibers inhaled many years before. On the other hand, small, thin bodies, though doubtless of recent formation, are no indication that their central fibers have been recently inhaled. "Young" bodies may be encountered in sputum from persons who have had no opportunity

of inhaling dust for many years, and it is known that asbestos fibers may remain in the lung for long periods without necessarily becoming converted into "bodies" at all.

Another point of great importance is the so-called "weathering" of the asbestos body. Many of the old large bodies present a distinctly ragged or weather-beaten aspect, often consisting, as it were, of widely separated irregularly shaped beads strung on the fibrous core. There can be little doubt that this process is associated with solution and disintegration of "body" substance and accounts, in my opinion, for the interesting finding of Fowweather that the silica content of the fibrotic portion of the asbestos lung is much less in workers who have been away from dust for many years than in those recently or still in employment, even where the length of exposure has been the same. "Weathering" is probably a constant process in these cases, but may be accelerated by the occurrence of caseous or suppurative change.

The clump-like arrangement of bodies within the lung alveoli was observed from the very outset of detailed histologic studies (Stuart McDonald, 1927). When the presence of clumps in the sputum was first reported by Stewart, Tattersall and Haddow (1932) it was suggested that this finding was a clear indication of disintegration of lung tissue, whether by a process of simple suppurative bronchopneumonia or as a result of a secondary tuberculous infection. In either case it was regarded as being virtually diagnostic of an underlying asbestosis. In the present study, 10 cases in which clumps were present in the sputum tend to substantiate this view. Four of them suffered from superimposed tuberculosis. Two of these have died and the remaining 2 are now critically ill. One other patient in whose sputum a clump was demonstrated is considered as a probable case of superimposed pulmonary tuberculosis. Of the remaining 5 cases, 2 have died, 1 of cerebral softening, acute bronchitis and bronchopneumonia, the other of bronchitis and cardiac failure, both with underlying asbestosis. The remaining 3 are suffering with definite progressive pulmonary asbestosis, fully confirmed by clinical and radiologic examination.

While the presence of asbestos clumps in the sputum is probably indicative of lung destruction, the converse is by no means true, that is, the absence of asbestos clumps affords no assurance of pulmonary integrity. There are many cases in the present series in which there has been definite disintegration of the lung and yet no clumps have been demonstrated in the sputum. Other possible fallacies exist. More prolonged and more careful examination might have yielded a positive result, or roughness in handling may have caused the clumps to break up. Lastly and perhaps most important, the underlying pathologic condition in the lung may have led to chemical or physical dissolution of the clumplike arrangement so that when expectorated in the midst of caseous material or pus, the clumps may have disintegrated into their individual fibers.

Gardner and Cummings (1931) state that in guinea pigs tuberculous caseation causes the asbestos bodies present to lose their golden-yellow color; they also fail to give a Prussian blue reaction and later are apparently so completely disintegrated that not even a supporting fiber remains.

Elastic tissue in the sputum, irrespective of the underlying pathologic condition, has long been accepted as unequivocal evidence of lung disintegration. Rappaport (1929-1930) mentions that elastic tissue may appear in the sputum of patients who present only very mild signs of clinical activity. He refers to Durand, a French worker, who demonstrated elastic fibers in the sputum of tuberculous patients, both before and after the appearance of tubercle bacilli. The 3 cases of the present series in which elastic tissue has been demonstrated in the sputum illustrate several points of interest. In Case 5, the presence of the elastic fibers is difficult to explain. She had been exposed to asbestos dust, it is true, for the last 10 years, and during this time it is quite possible for a progressive pulmonary asbestosis to have developed. Yet only a solitary asbestos body was found on one occasion. There was no definite evidence of tuberculosis, but the possibility that this disease existed in an abacillary or prebacillary stage could not be excluded. In Case 20, the presence of elastic fibers is associated with a rapidly progressive form of uncomplicated pulmonary asbestosis. In Case 16, the presence of elastic tissue is associated with active tuberculosis and clearly indicates a state of definite disintegration. The underlying pulmonary lesion here is probably illustrated by Case 28, from which Figures 6 and 7 were obtained. These show, in sections of the lung, elastic tissue in the midst of caseous tuberculous material, in a similar form to that expectorated in Case 16.

A careful search for tubercle bacilli has been carried out in every sample of sputum obtained. Positive findings were present in 6 out of 8 cases of proven tuberculosis. The incidence of tuberculosis in this series is therefore 21%, exactly the same as that recorded by Wood and Gloyne (1931), but less than figure given by Ellman (1930-1931), 6 out of 17 cases. Bridge (1931) reports an incidence of 31.5% in fatal cases.

**Conclusions.** 1. The presence of asbestos bodies in the sputum is indicative merely of exposure to asbestos dust. If they are of large size it means that a long interval has elapsed since the onset of exposure.

2. The number of bodies in any given specimen is insignificant, but the presence of old and weathered bodies on repeated examinations strongly suggests that a definite pathologic process is in existence.

3. Clumps in the sputum are definite evidence of lung disintegration, but their absence does not mean that disintegration is not in process.

4. Elastic fibers are probably indicative of rapid lung destruction.

5. Elastic fibers may be present in the sputum in pure pulmonary asbestosis both with and without clumps, or in asbestosis with associated tuberculosis.

6. The routine examination of the sputum in cases of suspected pulmonary asbestosis is essential, as it plays a significant rôle in the clinical diagnosis.

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#### ACETYL- $\beta$ -METHYLCHOLIN (MECHOLIN). OBSERVATIONS CONCERNING ITS ACTION ON THE BLOOD PRESSURE, SKIN TEMPERATURE AND THE HEART, AS EXHIBITED BY THE ELECTROCARDIOGRAM OF HYPERTENSIVE PATIENTS.

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HUNT AND TAVEAU<sup>1</sup> were the first to prepare and determine many of the pharmacologic properties of acetyl- $\beta$ -methylcholin. Major and Cline<sup>2</sup> have synthesized it ("mecholin") by a process which has made it available in quantity. Recently studies of its pharmacology

have also been carried out by Simonart,<sup>3</sup> and Comroe and Starr.<sup>4</sup> Starr, Elsom, and Reisinger,<sup>5</sup> have made clinical investigations of interest; especially their observation that mecholin is useful in the treatment of peripheral vascular disease, that it terminates attacks of tachycardia, and that it reduces the level of the blood pressure when taken by mouth. It has therefore seemed desirable to study the effect of mecholin on the heart as measured by the electrocardiograph, to learn whether it is of therapeutic importance in the treatment of hypertension in patients, and to ascertain its effect on the skin temperature.

**Description of Response to Mecholin Subcutaneously Injected Into a Hypertensive Patient.** Almost immediately after 25 mg. of mecholin\* were injected subcutaneously the face began to flush and tears poured from the eyes. The pulse became more rapid and the flush deepened and extended progressively down over the chest and upper abdomen. Respiration became deep and slower. Beads of sweat then began to appear and collected until the patient was literally drenched. The blood pressure which had been 210/140 mm. Hg fell to 96/70 mm. Hg. The patient gave a few hacking coughs and complained of gripping pains in the epigastrium. She found difficulty in breathing and stated that her heart was pounding in an alarming fashion. Saliva drooled from her mouth and she felt choked. The flushing and perspiration extended down to her hands and feet but did not include them; rather they appeared cold and slightly bluish. Vomiting occurred and the reaction was immediately terminated by injection of atropin (gr.  $\frac{1}{100}$ ). The patient then complained of being cold.

This describes a typical but severe reaction. Most of our studies have been conducted employing doses of 10 mg., which produces a relatively mild and not seriously uncomfortable effect. It is our impression that hypertensive individuals respond more actively than do normal ones to mecholin, but that old individuals, especially when suffering from arteriosclerosis, respond sluggishly.

**Effect of Mecholin on the Mechanism of the Heart Beat (Electrocardiograph) and on the Size of the Heart.** Electrocardiographic records were taken just before and at 2-minute intervals after the injection of mecholin. The most characteristic change observed after doses of 10 mg., though it did not occur in all subjects, was inversion of the *T* wave in all three leads. No change in *A-V* conduction time was noted in any of the records. The rate of the heart (Fig. 1) was always markedly increased. Atropin (gr.  $\frac{1}{100}$ ) not only terminated the action of the mecholin but also appeared to cause the *T* wave to resume its upright position. Evidently the action of the drug is not primarily on the cardiac muscle. Mecholin given by mouth in dosages of 1 gm. produces no changes measurable

\* We are very grateful to D. R. T. Major of the Laboratories of Pure Research (Merek & Co.) for a large supply of mecholin.

by the electrocardiograph. The records were taken at 30-minute intervals for a 2-hour period.

TABLE 1.—EFFECT OF MECHOLIN, SUBCUTANEOUSLY ADMINISTERED, ON THE HEART AS MEASURED BY ELECTROCARDIOGRAMS.

Patient.	Time.	Blood pressure.	Change in T wave.			Electrocardiogram conduction time.	R wave.	Other findings.
			T <sub>1</sub> .	T <sub>2</sub> .	T <sub>3</sub> .			
Essential hypertension Dec. 15th	3.22	218/150	+	+	±	0.16	....	Left ventricular preponderance.
	3.24	Mecholin 10 mg.						
	3.26	140/70	+	+	—	0.16	R <sub>s</sub> low voltage	
	3.28	145/100	+	+	—	0.16	R <sub>s</sub> low voltage	
	3.29	170/110	—	+	—	0.16	R <sub>s</sub> low voltage	
Nov. 16th	10.30	196/128	+	+	+	0.15	....	Left ventricular preponderance. Ventricular preponderance absent.
	10.37	Mecholin 10 mg.						
	10.40	140/80	—	—	—			
	10.45	140/84						
	10.48	140/86	Same	but	rate more rapid			
Latent hemor. Bright's disease Nov. 20th	10.02	190/120	+	+	+	0.18		T waves flattened.
	10.04	Mecholin 10 mg.						
	10.05	....	Same	but	pulse	more rapid.		
	10.06	120/70	—	—	—			
	10.08	144/102						
Essential hypertension	10.35	260/150	+	+	+	0.18	....	Left ventricular preponderance.
	10.36	Mecholin 10 mg.						
	10.37	Same	but	more	rapid pulse			
	10.38	190/120						
	10.40	Same	but	lower	voltage in S <sub>3</sub>			
Hemor. Bright's disease Nov. 14th	10.41	210/130						Left ventricular preponderance. Rate more rapid.
	10.58	158/106	+	+	—	0.21		
	11.00	Mecholin 20 mg.						
	11.01	110/55						
	11.02	90/45	+	+	—	0.20	R <sub>s</sub> split	
	11.08	80/20	+	+	—	....	U wave	
	11.10	88/48						
	11.13	80/40						
	11.13	Atropin gr. 1/125						
	11.20	146/110						
Hemor. Bright's disease	9.32	204/132	+	+	+	0.15	Low voltage and split.	
	9.34	Mecholin 10 mg.						
	9.36	160/70						
	9.37	....	—	+	—	....	Higher voltage.	
	9.38	110/60	—	+	—			
	9.40	Atropin gr. 1/100						
	9.42	150/110	±	+	+	....	Low voltage and split.	
Hemor. Bright's disease	4.12	190/110	+	+	—	0.15	....	Left ventricular preponderance.
	4.14	Mecholin 15 mg.						
	4.15	100/60	+	+	0	0.16		
	4.16	Atropin gr. 1/100	—	—	—	0.17		
	4.17	108/65						
	4.23	Atropin gr. 1/100						
	4.24	150/110						
	4.25	....	±	±	—	0.18		

The size of the heart studied in Roentgen ray photographs, taken at minute intervals for a period of 5 minutes following injection, shows no striking change, although after 1 minute a definite but small decrease followed by a slight increase was noted. The cardiac



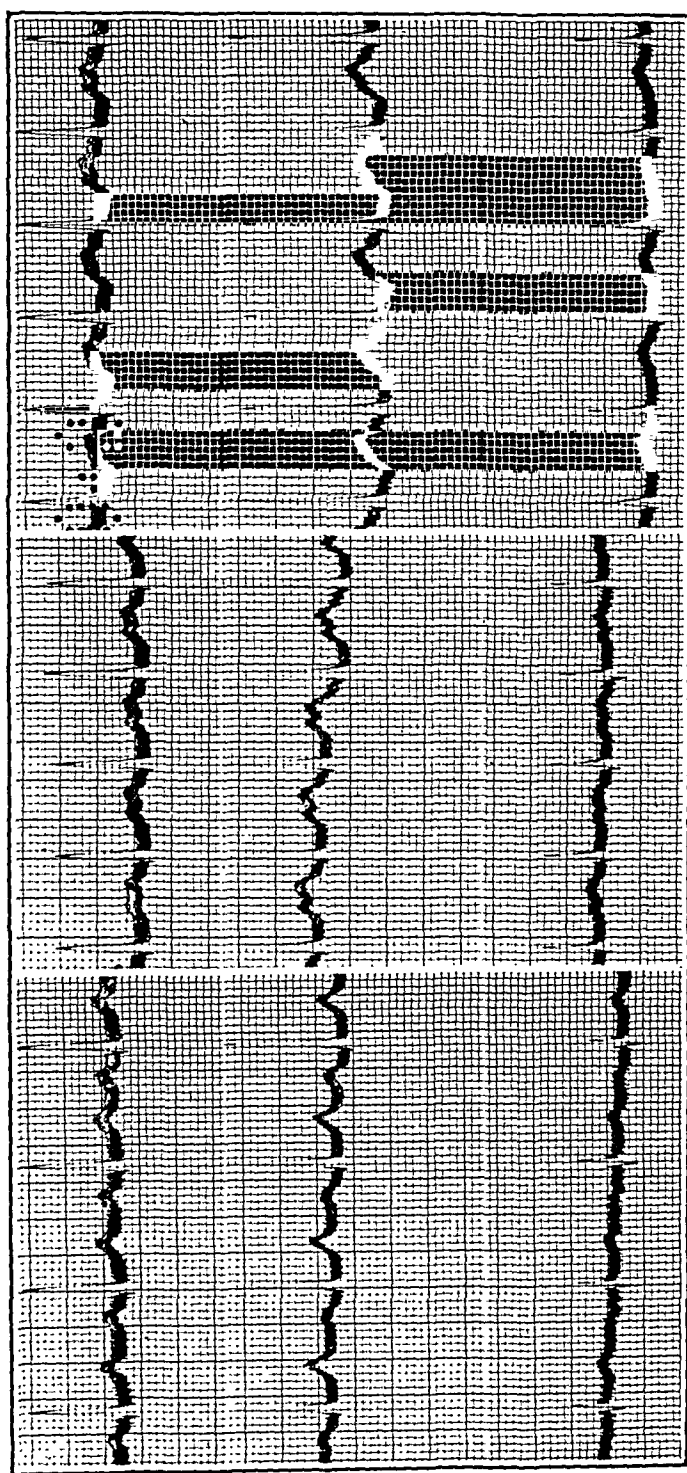


Fig. 1.—Inversion of the T wave following mecholol injection (Patient No. 3). (1) Control period (B. P. = 190/120); (2) 2 minutes after 10 mg. mecholol subcutaneously; B. P. = 120/70; (3) 4 minutes after mecholol; B. P. = 144/102.

shadow shows these changes\* in size: Control, 122.2 sq. cm.; 1 min. after mecholin, 110.2 sq. cm.; 2 min., 120.7 sq. cm.; 3 min., 136.6 sq. cm.; 4 min., 130.6 sq. cm.; 5 min., 135.2 sq. cm.

**Effect of Mecholin Administered by Mouth on the Level of the Blood Pressure.** Mecholin in doses of 0.9 gm. administered by mouth decreases the blood pressure slightly in hypertensive subjects. The action is variable, in some patients no reduction occurred.

TABLE 2.—EFFECT OF MECHOLIN TAKEN BY MOUTH.

Patient.	Diagnosis.	Time.	Blood pressure.	Pulse.
Conlin	Hemorrhagic Bright's disease	2.35	148/100	82
		2.40	142/102	84
		2.45	142/100	82
		2.46	Mecholin 0.4 gm. given	
		2.56	142/86	82
		3.06	140/96	84
		3.20	142/90	80
		3.30	142/94	88
		3.45	144/94	90
		4.00	148/94	88
		5.25	148/96	88
Gordon	Essential hypertension	9.30	160/104	74
		9.40	164/106	76
		9.50	162/104	74
		9.55	Mecholin 0.9 gm. given	
		10.05	154/104	72
		10.15	110/90	70
		10.25	134/88	68
		10.40	160/110	70
		11.25	170/104	78

Mecholin has been given to 2 patients suffering from essential hypertension (blood pressure: systolic 220, diastolic 130 mm. Hg; and systolic 260, diastolic 150 respectively) and in 2 with hypertension resulting from hemorrhagic Bright's disease (blood pressure: systolic 156, diastolic 102; and systolic 160, diastolic 110 respectively). They had remained in bed for several months and the level of the blood pressure had become stationary. They were well accustomed to experimental procedures. The measurements of the pressure were ordinarily made  $1\frac{1}{2}$  hours after the first dose of mecholin. The administration of amounts of mecholin up to 2 gm. (divided into 3 doses) had no effect on the level of their average blood pressure. Four grams daily (divided into 3 doses) were given to 1 of the patients for a period of 4 days, without effect. Large doses may cause transient reductions but the average level remains unchanged in the hypertensive subject.

**The Effect of Mecholin on the Skin Temperature of Hypertensive Patients.** The skin of the face and trunk when mecholin was administered subcutaneously, exhibited marked vasodilatation, but the hands and feet usually remained uninvolved. It seemed

\* The area, traced on paper, is measured with a planimeter.

desirable therefore to repeat this observation and to measure the temperature of the skin.\*

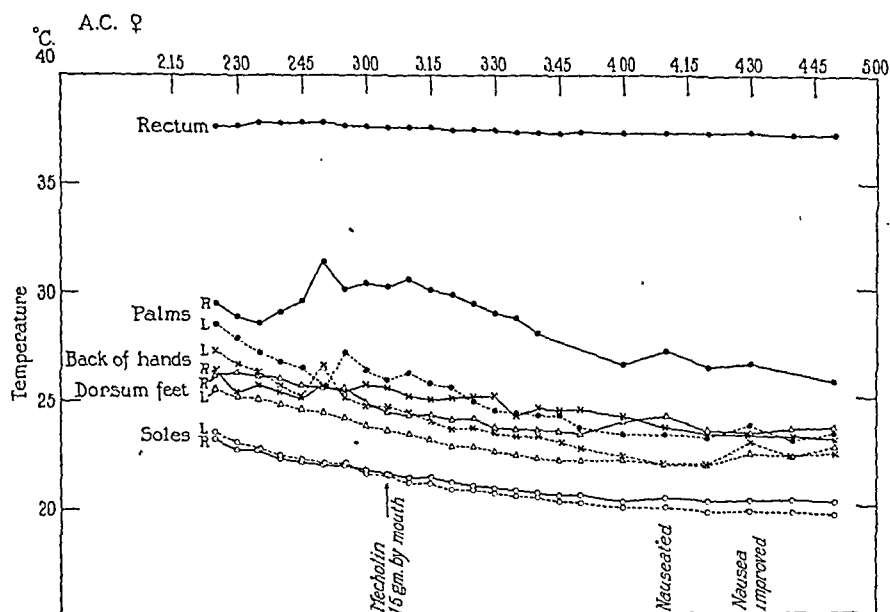


CHART I.—The effect of mecholin administered by mouth on skin temperature of hypertensive patients.

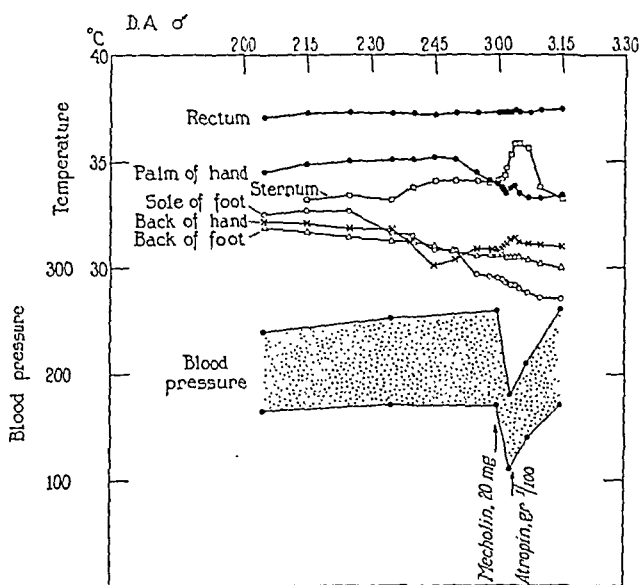


CHART II.—The effect of intramuscular injection of mecholin on skin temperature of hypertensive patients.

\* These experiments were performed by Dr. J. Murray Steele. Dr. Steele will describe his modification of the Benedict thermocouple later.

Modified Benedict multiple thermocouples were employed for the purpose, placed on the chest, hands, feet, and in the rectum. The temperature of the room was constant, the normal fluctuations in the temperature of the skin were first recorded. Mecholin 10 to 15 mg. was then administered subcutaneously. The superficial vessels of the face and thorax dilated maximally. A corresponding rise in temperature occurred. The skin of the palms and backs of the hands, however, as well as of the dorsal and plantar surfaces of the feet, exhibited slight if any significant change. Oral administration also appeared to have no significant effect.

**Discussion.** One cannot but be impressed by the resemblance of the reaction to mecholin to that following the injection of pituitrin and pilocarpin into the cerebral ventricles. Cushing<sup>6</sup> observed that the injection of 1 cc. of pituitrin promptly caused intense flushing, profuse perspiration, lachrymation, retching and vomiting, salivation, marked fall in body temperature, coincidental lowering of the basal metabolic rate. These reactions occur in the absence of significant pupillary change, pilomotor action or stimulation of the lower bowel. The response to pilocarpin was similar except that (1) more marked vagal effect was noted with continued retching and vomiting and (2) the fall in body temperature was more marked and enduring.

These results suggest that when these drugs are introduced into the cerebral ventricles they do not act on the periphery through the medium of the circulating blood but depend for their action on impulses which travel from higher centers by way of the peripheral nerves. The reactions are similar to those following stimulation of the parasympathetic centers in the hypothalamus. They resemble furthermore attacks observed by Penfield<sup>7</sup> in a patient suffering from what he has described as "diencephalic autonomic epilepsy." Sudden vasodilatation of the skin area supplied by the cervical sympathetic chain occurred at the initiation of the attacks. This was followed by lachrymation, diaphoresis, salivation, retardation of respiratory rate and rarely loss of consciousness. The irritative source of the attacks was an encapsulated tumor which periodically pressed on the thalamus of both sides. This syndrome differs from that following mecholin in that the blood pressure rises sharply while in the latter the pressure falls precipitously.

In certain respects the reaction to mecholin differs from that usually observed following certain types of stimulation of the hypothalamic centers.<sup>8</sup> The first difference already mentioned lies in the fact that the blood pressure falls after mecholin administration, whereas ordinarily a rise is noted following stimulation of the hypothalamus. Vasodilatation is, however, the more usual parasympathetic and vasoconstriction the sympathetic reaction. To what extent the central mechanism is involved in vasodilatation is unknown but it seems certain that it plays an important part.

TABLE 3.—COMPARISON OF THE SIGNS AND SYMPTOMS RESULTING FROM MECHOLIN ADMINISTRATION WITH THOSE RESULTING FROM STIMULATION OF THE HYPOTHALAMIC CENTERS.

Pituitrin intraventricular.	Pilocarpin intraventricular.	Histamin intraventricular.	Stimulation of "parasympathetic centers."	Diencephalic epilepsy.	Mecholin intramuscular.
Slight rise in blood pressure Nausea Marked flush Perspiration	Slight rise in blood pressure Nausea, vomiting Marked flush Perspiration	No change Nausea No flush Slight perspiration	Uncertain Nausea, vomiting Marked flush Perspiration	Marked rise in blood pressure ..... Marked flush Perspiration	Fall in blood pressure Nausea, vomiting Marked flush Perspiration
Lachrymation Salivation Temp. fall Sl. slowing of pulse	Lachrymation Salivation Temp. fall Sl. slowing of pulse	No lachrymation No salivation Sl. temp. fall No change in pulse	Lachrymation Salivation Temp. fall Slowing of pulse	Lachrymation Salivation Temp. fall Increased pulse rate	Lachrymation Salivation Temp. fall Increased pulse rate
No change in pupillary size Counteracted by atropin and tribromethanol Fall in basal metabolism	No change in pupillary size Counteracted by atropin No m'rk'd change in basal metabolism	..... ..... Slight rise	Constriction of pupil ..... Decrease in basal metabolism	Dilatation or contraction of pupil .....	No consistent change in pupil Counteracted by atropin
.....	.....	Severe headache	.....	.....	No headache

A second point concerns the pulse rate. Parasympathetic stimulation usually leads to slowing of the heart rate but with mecholin this result is either transient or is not observed at all. It is possible that fall in blood pressure stimulates the sympathetic system reflexly enough to overcome the parasympathetic effect or does so directly. That the vagus nerves are stimulated, however, and not the muscle, may be surmised from the fact that inversion of the *T* waves in the electrocardiogram disappears on injection of atropin.

The peripheral dilatation of the bloodvessels is a matter of especial interest. It is first observed in the face, spreads down the neck, over the chest, but usually does not extend much below the umbilicus. The upper arms are involved and the legs to a much smaller degree. The feet and hands exhibit slight and transient flushing, but at times appear cyanotic. Active perspiration occurs approximately in the same areas as flushing and parallels its intensity. The reaction is striking; intensely red, perspiring faces and necks, distal portions of hands and feet often dry and dusky. It resembles that following the administration of amyl nitrite. Amyl nitrite, as Filehne<sup>9</sup> showed many years ago, produces dilatation by acting on certain centers in the brain, for when the vessels from the brain are clamped, no dilatation of the vessels of the rabbits' ears occurs, although the blood in the ears contains the drug. Conversely, when the circulation is intact and amyl nitrite is present in the cerebral blood, dilatation of the ear vessels occurs even if the ear is perfused with blood from another source free of amyl nitrite.

Mecholin like cholin acts also on the peripheral portion of the vascular bed. Decerebration of etherized cats does not abolish

the muscarin-like action. The fall in pressure is indeed often greater than before. But such experiments on anesthetized animals are not comparable to those on man.

Mecholin when injected subcutaneously into man seems then to have a powerful stimulating effect on the cerebral parasympathetic centers, presumably those in the anterior group of nuclei of the diencephalon—Cushing's "neurohypophyseal mechanism," which accounts for its ability to simulate so closely the signs and symptoms which arise either from direct electrical stimulation, from stimulation by the intraventricular injection of drugs, or from stimulation due to irritation by tumors. It is possible that the premotor area of the cerebral cortex also forms a part of the stimulated area. Recent data of Kennard<sup>10</sup> indicate that this area directly influences the autonomic nervous system and in particular the vasomotor mechanism.

The fact that dilatation of the bloodvessels occurs to a slight extent only in the hands and feet is a disappointment from the viewpoint of therapeutics. The rise in temperature is inconsequential and does not lead to the belief that marked therapeutic benefit can be derived from its administration. Starr has observed encouraging results from its use in Raynaud's disease, however. The fact that no marked changes occurred in the temperature of the skin of our patients suffering from arterial hypertension should not discourage its thorough clinical trial, as Starr recommends.

It is surprising to discover that the reaction to mechohin simulates an exaggerated blush. Heightened beating of the heart, flushing of the skin, drenching perspiration, the Rabelaisian effect of fright upon the bowel, the secretion by the lachrymal gland, all these are prominent characters in natural emotion. Mecholin induces this expression of the emotions without being accompanied by the emotions themselves. Evidently processes identified with the expression of emotions are secondary to or dependent on the behavior of the vascular and visceral organs and exist or can be called into existence without the need, as James, Lange and Sergi thought, of experiencing the emotion itself.

**Conclusions.** 1. Mecholin (acetyl- $\beta$ -methylcholin), administered subcutaneously, greatly increases the temperature of the skin of the face and trunk of patients suffering from arterial hypertension; the hands and feet usually remain almost unaffected. Administered by mouth it fails to have this action.

2. Doses of 4 gm. taken by mouth have either no effect on the average blood pressure, or a slight one only.

3. When administered subcutaneously, mechohin usually causes inversion of the *T* waves of the electrocardiogram; this effect may be abolished by injecting atropin. Except for increasing the rate no other characteristic action of mechohin on the heart, as observed in the electrocardiograph, was seen. The size of the heart may first be

decreased and then increased briefly, the increase occurring when the level of the blood pressure has fallen markedly.

4. Comparison of the clinical phenomena due to injection of mecholin with those observed in patients suffering from diencephalic epilepsy, or in patients in whom pituitrin or pilocarpin had been injected into the cerebral ventricles, demonstrates a striking similarity between them. It has been suggested that many of the effects of mecholin are due to stimulation of the diencephalic parasympathetic centers, and possibly the premotor area of the cerebral cortex.

5. Mecholin causes most of the prominent corporal characters in the play of natural emotions to appear without being accompanied by the psychical counterpart itself.

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### SO-CALLED HEMORRHAGIC ENCEPHALITIS AND MYELITIS SECONDARY TO INTRAVENOUS ARSPHENAMINS.\*†

BASED ON A REVIEW OF 158 CASES.

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CENTRAL nervous symptoms secondary to the intravenous administration of arspenamin were first reported in 1911 (Almkvist,<sup>1</sup> Fischer,<sup>2</sup> Kannengiesser<sup>3</sup>). More clearly to define this clinical picture and its prognosis, as well as to offer some facts about its

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† Complete bibliography in authors' reprints.

etiology, prophylaxis and medical and surgical therapy, we have analyzed 155 cases from the literature and added 3 personally observed cases. In this analysis all questionable and borderline cases have been eliminated. There were 146 cases of encephalitis,<sup>1-112</sup> 8 of myelitis<sup>113-120</sup> and 4 of encephalomyelitis.<sup>121-123</sup> The meninges were involved in 33 cases, 30 being examples of meningo-encephalitis, 2 of meningomyelitis and 1 of meningoencephalomyelitis. There were 120 deaths (a mortality of 76%), with 98 autopsies. In spite of this high mortality, these reactions occur infrequently, and for this reason one should not be influenced against the proper use of arsphenamins. Statistical studies indicate these reactions occur once in every 6500 cases, and once in every 36,000 injections. A multiplicity of terms has been used to describe this syndrome, such as cerebral purpura, serous apoplexy, hemorrhagic encephalitis, medullary perivascular necroses, toxic myelopathy and toxic myelitis.

TABLE 1.—TOXIC REACTIONS.

	No. of cases.	Injections.	Complications.	Deaths.
German, 1914 <sup>10</sup> . . .	74,018	288,942	642	56
German, 1917 <sup>10</sup> . . .	265,168	268,946	..	70
Cologne, 1920 <sup>125</sup> . . .	...	225,780	..	12
Civil England <sup>10</sup> . . .	77,645	298,011	77	10
British Military Hosp. <sup>10</sup> .	4,887	39,036	126	3
British Military Hosp. <sup>10</sup> .	18,500	125,000	250	10
U. S. Navy, 1925-29 <sup>76-80</sup>	16,075	257,789	282	20
Total . . . . .	456,293	1,503,504	1377	181

The above statistics show that (omitting the second and third series) 191,125 patients receiving 1,108,778 injections of arsphenamin compounds had 1377 complications. One complication occurred in every 129 cases and in every 804 injections. One death occurred in every 2699 cases and in every 14,384 injections. Of this total number of deaths, about 50% were due to central nervous system lesions. There was approximately 1 death secondary to central nervous system involvement in every 5398 cases, and in every 28,768 injections. Of the remaining 50% of deaths, most were caused by exfoliating dermatitis and acute yellow atrophy of the liver; in rarer instances, by acute hemorrhagic nephritis, ulcerative enteritis and aplastic anemia.

Hemorrhagic encephalitis was first described by Rosenfeld,<sup>126</sup> in 1903. In 1905, a more thorough pathologic investigation was carried out by Schmidt,<sup>127</sup> who substituted the term "brain purpura." In 1913, Oeller,<sup>128</sup> attacked the term "hemorrhagic encephalitis." Alpers,<sup>129</sup> who reviewed the subject in 1928, believed that hemorrhagic encephalitis was a poor term because the hemorrhage was not an important part of the process, and it was not inflammatory, as the term "encephalitis" would imply. "Brain purpura"



was also inadequate because the pathology was not a purpura, but merely a purpuric rash. "Serous apoplexy" was not a good term because it did not explain the picture in all cases. He suggested the term "medullary perivascular necroses." The foci of hemorrhagic encephalitis have been reported in association with numerous other conditions, such as phosgene or carbon monoxid poisoning, grippe, pneumonia, tuberculous meningitis, malaria, typhus fever, cerebral trauma, pernicious anemia, secondary anemia, erythema multiforme, psoriasis, scurvy, cerebral thrombosis or embolism and meningovascular syphilis, or secondary to circulatory disturbance caused by hemorrhage, thrombosis and tumor.

**Case Abstracts.** CASE 1.—A male, aged 29, complained of sore throat and painful, swollen cervical lymph glands, April 10, 1932. His past and family histories were negative. Two days later, a diagnosis of Vincent's angina and acute cervical adenitis was made, and he was given 0.15 gm. of neoarsphenamin intravenously without any reaction. On the 4th day after admission to hospital he was given 0.3 gm. of neoarsphenamin intravenously. On the 6th day he developed a hemorrhagic nephritis, and on the 7th day, an intense erythema of the skin of the entire body. On the 8th day the patient complained of a headache, vomited, became disoriented, irrational and comatose. He developed generalized convulsions and had a complete loss of sphincter control. Temperature range was 97.6° to 104.6° F. Pulse and blood pressure within normal limits. Neurologic examination on the 12th day revealed a stiff neck, bilateral Babinski, positive Kernig, abdominal reflexes were absent and deep reflexes normal. Pupils were contracted and did not react to light. Fundus vessels were congested. *Laboratory reports:* Urine contained albumin, numerous red and white blood cells and many hyaline and granular casts. White blood cells ranged from 6500 (38.5% neutrophils) to 24,000 (65% neutrophils). The blood Wassermann test was negative. The blood non-protein nitrogen varied from 43 to 49 mg. per 100 cc. Spinal fluid on the 12th and 13th days showed increased pressure, otherwise negative. Treatment was used for the Vincent infection, hot Epsom salt packs for the swollen lymph glands, morphin and codein, allonal and sodium amytal as analgesics and sedatives. Further treatment: 10 cc. of 10% sodium thiosulphate intravenously, 3 times daily, and 50 cc. of 50% glucose in saline intravenously, 3 times daily, normal saline hypodermoclysis, 1% glucose solution per rectum and 3 lumbar punctures. *Course:* On the 14th day the patient partially recovered consciousness and recognized objects. He improved steadily, and on the 16th day he regained full consciousness. On the 22d day he had entirely recovered.

CASE 2.—A male, aged 35, complained of headaches, nausea and vomiting on March 30, 1933. His past and family histories were negative. The patient had received 4 doses of arsphenamin at weekly intervals for a skin eruption, the exact amount not ascertainable. On the day after the 4th dose the patient developed headache, with nausea and vomiting, and finally lapsed into a state of coma, remaining so for approximately 48 hours. The 3d day he developed a papular rash. He was seen on the 4th day. Neurologic examination revealed the patient in a stuporous condition; he could be aroused but quickly lapsed into unconsciousness. The pupils were slightly irregular, there was a failure of convergence and a lateral nystagmus on looking to the right. There was some difficulty in his upward gaze and a slight weakness of the right arm. Abdominal, cremasteric, patellar and Achilles reflexes were absent. *Laboratory reports:* Leukocytes, 4100;

neutrophils, 84.5%; hemoglobin, 90%; erythrocytes, 5,168,000. Urine, albumin present; on 4th day, positive for bile pigment. Spinal puncture, clear colorless fluid; pressure, 190 mm.; cells, 7 per c.mm.; globulin, slight increase; sugar, 74 mg. per 100 cc. Wassermann test negative. Under dehydration therapy, consisting of limitation of fluids and 50 cc. of 50% glucose intravenously, every 3 hours, and sodium thiosulphate, the 2d day following these injections his headache was entirely absent and he was perfectly conscious. Several days later he developed hepatitis with jaundice and evidence of acute nephritis as indicated by the red cells in the urine. Within 2 weeks he had entirely recovered and left the hospital.

TABLE 2.—INCIDENCE OF DISEASES TREATED WITH ARSPHENAMINS.

	No. of cases.	Percentage.
Syphilis . . . . .	135	93
Vincent's angina . . . . .	1	1
Pneumonia . . . . .	1	1
Psoriasis . . . . .	1	1
Skin eruption . . . . .	1	1
Not stated . . . . .	7	3
Total . . . . .	146	

The occurrence of these reactions in non-luetic cases readily rules out the theories that attempt to place their occurrence upon a luetic basis.

TABLE 3.—AGE INCIDENCE.

Year.	No. of cases.	Percentage.
1 to 9 . . . . .	3	2.0
10 to 19 . . . . .	18	12.0
20 to 29 . . . . .	59	40.0
30 to 39 . . . . .	25	17.0
40 to 49 . . . . .	10	5.0
50 to 59 . . . . .	2	1.0
Not stated . . . . .	28	22.5
60 to 70 . . . . .	1	0.5
Total . . . . .	146	

The prevalence of this reaction in the third and fourth decade is without doubt due to the prevalence of syphilis during this period.

TABLE 4.—SEX INCIDENCE.

	No. of cases.	Percentage.
Males . . . . .	89	60
Females . . . . .	44	30
Not stated . . . . .	13	10
Total . . . . .	146	

Little emphasis need be placed on the predominance of these reactions in males, as we may assume males are more frequently afflicted with syphilis.

TABLE 5.—TOTAL DOSAGE OF ARSPHENAMINS USED BEFORE ONSET OF SYMPTOMS.

	No. of cases.	Percentage.
0.05 to 1.1 grams . . . . .	78	53
1.10 to 2.1 " . . . . .	44	30
2.10 to 5.6 " . . . . .	17	11
Not stated " . . . . .	7	6
Total . . . . .	146	

When these toxic reactions were first described, it was the opinion that the dose of arspphenamin was too high, and for this reason smaller doses were recommended. Table 5 clearly demonstrates the falsity of this opinion and also that the quantity of the arspphenamin injected is not in any way related to the occurrence of symptoms.

TABLE 6.—NUMBER OF DOSES GIVEN BEFORE ONSET OF TOXIC SYMPTOMS.

	No. of cases.	Percentage.
1 . . . . .	19	13.0
2 . . . . .	72	50.0
3 . . . . .	23	15.0
4 to 9 . . . . .	26	17.0
9 to 15 . . . . .	1	0.5
Not stated . . . . .	5	4.5
Total . . . . .	146	

In 50% of the cases, hemorrhagic encephalitis followed the second injection. The significance of this fact we are unable to state.

TABLE 7.—TIME OF ONSET OF SYMPTOMS AFTER LAST DOSE.

	No. of cases.	Percentage.
Not given . . . . .	42	31.0
1 to 12 hrs. . . . .	13	9.0
12 to 24 " . . . . .	24	16.0
24 to 38 " . . . . .	22	15.0
48 to 72 " . . . . .	21	14.0
72 to 144 " . . . . .	16	11.0
7 days . . . . .	1	0.5
9 " . . . . .	1	0.5
10 " . . . . .	1	0.5
12 " . . . . .	1	0.5
21 " . . . . .	1	0.5
56 " . . . . .	2	1.0
70 " . . . . .	1	0.5
Total . . . . .	146	

These reactions occur more frequently within the first three days after injection.

Hemorrhagic encephalitis in certain cases is so rapidly fatal that therapy is of no avail. In approximately 20% of the cases, death occurred within the first 24 hours. The time of death in the re-

maining cases varied from 2 to 35 days, thus the importance of an early diagnosis cannot be overemphasized.

TABLE 8.—TIME OF DEATH AFTER ONSET OF TOXIC SYMPTOMS.

	No. of cases.	Percentage.
1 day . . . . .	23	20
2 days . . . . .	18	15
3 " . . . . .	15	13
4 " . . . . .	4	4
5 " . . . . .	1	1
6 " . . . . .	4	3
7 " . . . . .	2	2
8 " . . . . .	1	1
35 " . . . . .	1	1
Not stated . . . . .	45	40
Total . . . . .	114	

TABLE 9.—SYMPTOMS (146 CASES).

	No. of cases.	Percentage.
Headaches . . . . .	58	40
Vomiting . . . . .	55	38
Nervousness . . . . .	14	9
Chills . . . . .	12	9
Dizziness . . . . .	10	8

It may be noted that headache, vomiting, chills, nervousness and dizziness occurred in the majority of these cases, whereas the following group of symptoms occurred in less than 5%: Perspiration, backache, fatigue, numbness, aphonia, dyspnea, dysphagia, photophobia, anorexia, hiccough, cough, body pains, diarrhea and diplopia. These predominating symptoms of headache, vomiting, dizziness are characteristic of increased intracranial pressure.

TABLE 10.—PHYSICAL SIGNS.

	No. of cases.	Percentage.
Fever . . . . .	61	41
Respiratory changes . . . . .	28	19
Cyanosis . . . . .	26	17
Pulse changes . . . . .	24	16

The physical signs are primarily: Increased temperature, pulse and respiratory changes and cyanosis, all indicative of toxic reaction. In addition to these symptoms, and occurring in less than 5% of the cases, are oliguria, anuria, skin rash, flushing of the skin, icterus and enlargement of the lymph glands. In all probability, fever occurred in more than 41% of the cases. Many of the records failed to mention the temperature status. Respiratory changes consisted of Cheyne-Stokes breathing, rapid respiration or paralysis.

Of the 146 patients, 80% had convulsions; 79% of them were unconscious. In a lesser degree, the various eye changes occurred which consisted of involvement of the 3d, 4th, 6th and 8th cranial

nerves. Hyperactive, hypoactive, absent and pathologic reflexes occurred in 30%. Meningeal signs, such as opisthotonos and rigidity of the neck, took place in approximately 13%. Such symptoms as generalized body rigidity, staggering gait, sensory disturbance, chewing movements, fibrillary tremors, excessive salivation and aphasia were reported. Mental disturbances consisting of delirium, disorientation as to time, place and person are found in less than 50%.

TABLE 11.—NEUROLOGIC SIGNS.

	No. of cases.	Percentage.
Convulsions . . . . .	117	80
Unconsciousness . . . . .	116	79
Pupillary and extraocular muscle changes . . . . .	58	39
Reflex changes . . . . .	45	30
Loss of sphincter control . . . . .	32	21
Mental disturbance . . . . .	29	20
Hemiparalysis of face, arms, legs . . . . .	24	16
Rigidity of neck . . . . .	19	13

TABLE 12.—LABORATORY STUDIES.

	No. of cases.	Percentage.
Laboratory work not stated . . . . .	60	41
Laboratory work stated . . . . .	86	59
Urine examinations reported . . . . .	47	
Acute nephritis . . . . .	17	35
Albumin . . . . .	6	11
Normal . . . . .	24	54
Lumbar puncture . . . . .	39	
Pressure normal . . . . .	6	16
Pressure increased . . . . .	25	63
Not stated . . . . .	8	21
Globulin increased . . . . .	23	58
Red cells . . . . .	10	26
White cells . . . . .	24	63
Negative Wassermann . . . . .	7	16

Of the 86 cases with laboratory data, 46% showed evidence of renal trouble—an indication of the diffuse nature of the lesion. The increase in spinal fluid pressure in 63% of 39 cases indicates that an increase of intracranial pressure is a salient feature of this disease. Subarachnoid hemorrhage was definitely indicated in 26% of the cases.

*Myelitis.* Toxic myelitis or myelopathy<sup>115</sup> without any demonstrable involvement of the brain is extremely rare. In the 22 cases of cord involvement that we have been able to collect from the literature, 8 had myelitis and 4 encephalomyelitis; 1 of the latter we have reported. In 11 cases of encephalitis, cord involvement occurred as a pathologic finding without clinical symptoms. The first case of myelitis following the intravenous injection of arsphenamin compounds was reported in 1911.<sup>115</sup> In this country Newmark<sup>130</sup> and Veck<sup>131</sup> reported the first case (1911) of myelitis following the use of arsphenamin intramuscularly. Davidson and Kerschner<sup>132</sup>

feel that the term "myelitis" is very often employed to designate cases of diffuse non-systemic disease of the spinal cord in which the pathologic process bears no relation to infection, but is due to toxins, avitaminosis, vascular disease, trauma or compression. Many cases of so-called infectious myelitis are not cases of myelitis but represent a primary condition of the meninges or vessels with secondary changes in the cord which ultimately lead to myelomalacia. They believe that the term myelitis should be limited to inflammatory lesions of the cord and not degenerative. They prefer the term "toxic myelopathy" for the latter.

TABLE 13.—ANALYSIS OF DATA ON 8 CASES OF MYELITIS.

Author.	Sex.	Age.	Doses.	Total dose.	Onset of symp. after last inj., days.	Salient neurologic signs.	Treatment.	Outcome.	Lues.	Autopsy.
Zalkan <sup>112</sup>	M	24	2	1.5	1	Flaccid level lesion	Not stated	Not stated	Yes	
Bayet <sup>113</sup>	F	27	1	3.3	6	Level lesion, spastic	Not stated	Death, 6 mos.	Yes	Yes.
Chiari <sup>114</sup>	M	35	2	1.0	13	Level lesion, ascend.	...	Death, 17 days	Yes	Yes.
Fleischmann <sup>115</sup>	..	..	2	0.8	4	Level lesion, spastic	Hg; iod.	Slight improv.	Yes	
Juliusberg and Oppenheim <sup>116</sup>	..	15	1	0.2	6	Level lesion; men. signs.	Not stated	Not stated	Cong.	Yes.
Pechin <sup>117</sup>	M	35	3	..	1	Level lesion, flaccid	Novarsbenz. prog. 7 mo.	Comp. recov.	Yes	
Pinard <sup>118</sup>	M	23	1	1.8	2	Level lesion, flaccid	Not stated	Death, 2 wks.	Yes	Yes.
Scott and Reinhart <sup>119</sup>	M	..	1	0.6	8	Level lesion, spastic	Not stated	Persist.	No	

Inasmuch as we have only 8 cases of myelitis, 5.4% of all central nervous system cases, a statistical study would be of little value, but a table would serve to emphasize certain outstanding features of this condition. A small percentage of these cases had a rash or jaundice before onset of neurologic symptoms. In regard to sex, age, number of doses and total dosage, as well as the time of onset of symptoms after the last dose, those cases that develop a myelitis correspond to those that develop an encephalitis. The spinal cord lesion is one of massive involvement, usually ascending in type and either spastic or flaccid. In these 8 cases, only 1 made a complete recovery and, peculiarly enough, this case was given increasing doses of novarsenobenzol. Case 8 had a syphilophobia<sup>119</sup> and, in spite of all serologic studies being negative, demanded antiluetic therapy. Only 3 of this series came to complete autopsy, and the results of these are reported in detail in the original articles. The case reported by Newmark<sup>130</sup> and Vecki<sup>131</sup> following intramuscular arsphenamin also came to autopsy. The pathologic findings of the cases receiving intramuscular injections were the same.

In this series of 158 cases, there are 4 which manifest a combination of the clinical picture of an encephalitis and myelitis. This is 2.5% of total central nervous system cases. One of these cases, directly observed by us, is reported in detail.

*Encephalomyelitis.* CASE 3.—A male, aged 27, complained of sore throat, February 12, 1931. Past and family histories negative. Examination showed an acute ulcerative tonsillitis and smears revealed Vincent's organisms. He was given 0.15 gm. of neoarsphenamin intravenously. The 3d day, he developed retention of urine and was constipated. On the 6th day he noticed a peculiar abnormal sensation throughout his trunk and limbs. In the afternoon he received 0.15 gm. of neoarsphenamin intravenously. That night he had a fever, chills and hallucinations. On the 8th day he could not move his legs and had a generalized hypesthesia, and pain in the lumbar region that ascended to the thoracic region. On the 10th day he noticed weakness of the right arm and paresthesias in both hands. That afternoon the respirations became labored and the skin cyanotic. On the 12th day a lumbar puncture was performed, and in 24 hours the respiration improved. At this time he was seen in consultation. During the next 10 weeks he had involuntary urine and stools, and paraplegia of both legs; deep tendon reflexes of the arms active. Patellar and Achilles reflexes absent. There was a complete loss of sensation below the level of the 8th thoracic vertebra. Above the level of the 1st thoracic vertebra sensation was diminished. The temperature ranged from 98° to 102° F.; pulse, from 60 to 120; respirations, from 10 to 40. The blood Wassermann test was negative. The urine showed albumin and a few red blood cells. *Lumbar puncture* on the 12th day was clear and showed increased pressure, otherwise negative. On the 22d day pressure was markedly decreased, the fluid xanthochromic, with 10 cells. *Lumbar puncture* on the 60th day showed 20% block. Therapy, sedatives. *Course:* Levels of paralysis and sensation have not changed in 3 years; incontinence of urine and stools persist; no change in the reflexes.

TABLE 14.—THREE ADDITIONAL CASES OF ENCEPHALOMYELITIS FROM THE LITERATURE.

Author . . . . .	Feldman and Bratzlowsky. <sup>121</sup>	Gryzbrowsky. <sup>122</sup>	Socin. <sup>123</sup>
Sex . . . . .	M	F	F
Age . . . . .	36	32	38
No. doses . . . . .	3	3	2
Total dosage . . . . .	0.75 gram	0.75 gram	1 gram.
Onset after last injection	1 day	1 day	2 days.
Chills . . . . .	Yes	No	Yes.
Fever . . . . .	Yes	Yes	Yes.
Salient neurologic signs and symptoms . . . . .	Vomiting; convulsions; level lesion, atrophy; flaccid then spastic; sphincter disturbance	Unconscious; pupillary changes; level lesion; mening. signs	Headaches; pupillary changes; mental disturb.; convul.; level lesion; sphincter disturbance.
Rash . . . . .	Early	None	Early.
Treatment . . . . .	Cal-chlorid; adrenalin; venesection; Hg and bismuth injection	Not stated	Not stated
Outcome . . . . .	Level lesion persisted	Died in 6 days	Died in 14 mos.
Lues . . . . .	Yes	Yes	Not stated.
Laboratory . . . . .	Urine and spinal albumin	Urine and albumin	Spinal fluid cells incr.
Autopsy . . . . .	....	Myelitis; encephalitis; pneumonia	No.

There is nothing characteristic in these 4 cases in regard to the clinical symptoms other than that they were a combination of

the encephalitic and myelitic pictures. A point of interest, though of questionable significance, is that 3 of the 4 cases had an exanthematous rash previous to onset of toxic symptoms. Also in 3 of these cases, the cerebral symptoms occurred before the spinal symptoms. One case came to autopsy and had a combination of brain and cord lesions.

*Meningitis.* Many of these cases, in addition to having brain and cord disturbances, gave clinical signs of meningeal involvement, such as rigidity of the neck, opisthotonos and a positive Kernig. The question of meningeal involvement in cases of hemorrhagic encephalitis has not been particularly emphasized.

In 146 cases of encephalitis, 93 came to autopsy. Of these, 24 showed evidence of meningitis. Clinically, 30 showed evidence of meningitis, of whom 3 recovered.

TABLE 15.—PATHOLOGY.

Autopsy.	No. of cases.
Brain examined . . . . .	95
Cord examined . . . . .	21
Complete autopsy . . . . .	63
Total number autopsies . . . . .	98

In the cases of encephalitis, 98 had autopsies and, of these, 3 autopsies did not include the brain and cord. In the 8 cases of myelitis, 4 had complete autopsies. In the 4 cases of encephalomyelitis, 1 had a complete autopsy.

According to Alpers,<sup>129</sup> the majority of cases shows the following characteristics: The gross lesions appear as pinpoint, bright red discolorations throughout the brain substance. These may coalesce to form large foci and are usually found in the white matter (centrum ovale, corpus collosum and internal capsule), but occasionally in the gray matter (basal regions and thalamus), and in the pons and basal ganglia. Hemorrhage, however, is not an essential part of the picture. Microscopically, in the center of the lesion capillary or pre-capillary vessels are observed, with swollen or destroyed endothelium. In some instances, the swelling is so great as to completely obliterate the lumen. Often the lumen contains a fibrin clot or a hyaline thrombus. Immediately next to the central vessel is an area of necrosis, completely surrounded by a palisade-like arrangement of intact glial cells. Beyond the collar of glial cells, which are many layers deep, there may or may not be an outer area of hemorrhage. The cells which surround the central necrotic area are oligodendroglial. There are some fibrous neuroglia cells immediately outside these areas. These foci may occur without hemorrhage. Alpers<sup>129</sup> states that hemorrhage is apparently of little importance, as in most instances hemorrhages were not seen in relation to these areas despite the fact that grossly the lesions appeared discolored. The presence of red blood cells in these areas



is usually explained by diapedesis. Alpers found that thrombi in the central vessels (capillary or pre-capillary) occurred infrequently, and that the endothelium of the central vessels was swollen or destroyed, and the vessel often occluded by the swollen endothelium. He explains the origin of these foci as follows: As a result of the injury to the endothelium by a toxin or infectious process, neuroglia cells are collected about the vessel. As the blood supply is cut off through the occlusion of the vessel by the *swollen* endothelium, or possibly by a thrombus, the central cells in the area become destroyed and, as the process extends, a larger area of coagulation necrosis develops. Some cases<sup>17,63,76-80,89,98,110</sup> showed at autopsy hyperemia and edema of the brain without any areas of softening or hemorrhage. Stuhmer<sup>98</sup> believes that edema of the brain always occurs first, and in severe cases is always followed by hemorrhage. The increased intracranial pressure, as shown in 25 of the 39 cases upon which lumbar punctures were performed, also tend to stress the presence of edema of the brain. According to Scott and Reinhart,<sup>119</sup> the cord reveals a diffuse myelomalacia involving both the gray and the white matter, marked edema, degenerative lesions of the bloodvessels with perivascular hemorrhages, and complete destruction of all ganglion cells of the anterior horn. There is no exudate or glial proliferation.

TABLE 16.—INVOLVEMENT OF OTHER ORGANS IN COMPLETE AUTOPSIES.

Organs.	No.	Percentage.
Lungs . . . . .	27	42
Heart . . . . .	15	23
Liver . . . . .	11	17
Kidneys . . . . .	24	38
Spleen . . . . .	8	12
Stomach . . . . .	3	5
Intestines . . . . .	2	3
Thyroid . . . . .	1	1.5
Aorta . . . . .	1	1.5
Uterus . . . . .	1	1.5
Pancreas . . . . .	1	1.5
Skin . . . . .	1	1.5
All organs . . . . .	10	15
Larynx . . . . .	1	1.5
Bladder and ureter . . . . .	1	1.5

Examination of organs other than the central nervous system was carried out in 63 cases. Table 16 definitely reveals that pathologic changes existed in other organs, such as pinpoint hemorrhages, edema, cloudy swelling, fatty degeneration, congestion, all of these being caused by the arsphenamin reaction and being part of the generalized toxic reaction.

To date there have been numerous theories promulgated for the cause of arsphenamin central nervous system reactions, none of which particularly answers the problem.<sup>23,38,61,62,89,98,101,126,133-168</sup> They may be summarized as follows: (1) Action of the arsphenamin molecule itself, either by direct dilatation of the bloodvessels or by

indirect dilatation of the bloodvessels due to lack of adrenalin from destruction of the adrenal glands. The majority favors this theory. (2) Liberation of trivalent inorganic arsenic, due to faulty elimination of the drug due to kidney impairment. Ehrlich was the first to advance this theory. (3) Herxheimer reactions. May be ruled out in non-luetic cases. (4) Anaphylactoid reaction. (5) Allergic reaction. Schreiner<sup>165</sup> discusses the cutaneous disorders that develop in the course of arsphenamin therapy, such as the angioneurotic syndrome, the fixed arsphenamin exanthem, the generalized exanthem and the arsphenamin dermatitis. After calling attention to similarities between the cutaneous disorders resulting from arsphenamin therapy and the known allergic diseases, the author describes tests by which he attempts to prove the allergic character of the cutaneous disorders. In order to determine the presence of specific antibodies, he made cutaneous tests, and he was able to demonstrate the allergic nature of the symptoms in 18 of 20 patients presenting various forms of cutaneous disorders. (6) Uremia. Theory advanced by Stuhmer<sup>98</sup> and not mentioned by others. (7) Effects upon the reticulo-endothelial system.<sup>137,145,151</sup> Asuna and Kuhn<sup>137</sup> have shown a specific damage to the endothelial lining of the vessels. Hassko<sup>145</sup> believes that this damage is due to a defibrination of the blood. Experimentally he has shown that gelatin hinders these factors.

From the pathologic reports of the series of cases we have reviewed, it is apparent that there is a damage of the vessel walls. This is further substantiated by the work of Asuna and Kuhn,<sup>137</sup> Marschalko and Vezpremi<sup>151</sup> and Hassko.<sup>145</sup> Furthermore, similar changes have been found in cases that have died from organic arsenic poisoning; in addition, it must be remembered that this pathologic picture of so-called hemorrhagic encephalitis may be produced by the many other factors previously mentioned. It is apparent that the arsphenamin breaks down and eliminates free arsenic, as this was found in the organs in a number of these cases. Many explanations have been attempted to explain these facts, none being satisfactory, however. Why in certain people arsphenamin should be toxic and in others have no effect whatsoever is yet to be discovered. Furthermore, why the same patient, who has received arsphenamin 8 years (Bruhns and Löwenberg<sup>12</sup>) previously without developing any toxic reaction, then suddenly develops hemorrhagic encephalitis cannot be explained. Then, too, the same batch of drug has been used on a number of people, only 1 of the group developing symptoms. A case has been reported wherein the same ampule was divided between 2 patients (Miller<sup>66</sup>), injected at the same time; 1 of these developed a toxic encephalitis and the other did not. It is well known from reports of Newmark,<sup>130</sup> Vecki,<sup>131</sup> Fritz,<sup>169</sup> that this reaction may occur after intramuscular injection as well as intravenous injection. That it is not due to

syphilis is further emphasized by the 3 cases included in our reports, as well as the case of pneumonia treated by Henneberg.<sup>38</sup>

*Prognosis.* Of those with hemorrhagic encephalitis, 32 cases recovered; of those with myelitis, 1 recovered; and of those with encephalomyelitis, none recovered. Thus it appears that those patients with involvement of the spinal cord practically never recover, although they may live with a complete paraplegia after the symptoms have developed and die at a later time from a terminal infection. We have reviewed the encephalitis cases in hope of finding facts of prognostic value while the process is active. It is quite evident that the age, sex, total dosage of arsphenamin, number of doses of arsphenamin, time of onset of symptoms after the last dose and adjunct therapy did not in any way influence the progress of the disease.

It has been maintained by some authors, such as Scott and Moore,<sup>95</sup> Wechsellmann,<sup>105</sup> that the adjunct therapy used in conjunction with arsphenamin was responsible for the toxic reactions. In our review, mercurial preparations, iodids and bismuth, etc., did not in any way increase the toxicity of arsphenamin. In approximately 47% of these cases, adjunct therapy was utilized, and in 53% arsphenamins were given alone.

Apparently the reaction cannot be traced to any particular fault of the drug or any particular faulty administration of the drug. The following observations indicate conditions that may be considered signs of grave prognosis: All of the cases with hemiplegia died. In 27 cases with meningeal signs and symptoms, only 3 recovered. The prognosis is unfavorable for the first 3 days, after development of signs and symptoms, 48% of the patients dying in this period. In this series of cases those that recovered from hemorrhagic encephalitis did so completely and had no residual symptoms. The therapeutic measures may be divided into prophylactic and curative.

*Prophylactic Measures.* (1) Arsphenamins should not be given to patients with damaged kidneys.<sup>95,181</sup> (2) The best care and technique should be used in administering the drug.<sup>141,142,166</sup> (3) Ephedrin sulphate (50 mg.) should be given for 2 days previous to injection<sup>200</sup>. (4) Adrenalin, 1 cc. of 1 to 1000 intramuscularly 10 minutes before injection. (5) Atropin sulphate, grs.  $\frac{1}{150}$  hypodermically 15 minutes before the injection of arsphenamin.<sup>201</sup> Adrenalin, introduced by Milian, in 1912, has been used successfully by various writers.<sup>25,149,162,170-180</sup> It was Milian's belief that adrenalin insufficiency played a part in the causation of these symptoms. The vasodilator properties of these drugs in the presence of lessened adrenal activity lead to the production of these after effects, particularly upon the cerebral vessels. Rebaudi<sup>182</sup> recommended the use of amino-acids of the liver mixed with neoarsphenamin for patients who had an intolerance to the drug, especially as it permitted larger and more frequent doses of neoarsphenamin. He used

0.9 gm. of neoarsphenamin mixed with 2 cc. of amino-acid of the liver, stirring slowly with a glass rod until the color was yellow-gold.

*Curative Measures.* The curative measures may be given as follows: (1) *Against the toxic phenomenon:* (a) Adrenalin hydrochlorid, 1 cc. of 1 to 1000 intramuscularly followed by 1 cc. of 1 to 100,000 intravenously;<sup>154,180</sup> (b) sodium thiosulphate; (c) sodium dehydrocholate; (d) calcium thiosulphate; (e) calcium chlorid; (f) ephedrin sulphate; (g) 50% glucose solution. (2) *Sedatives:* Numerous sedatives have been utilized, such as chloroform, ether, morphin, codein, barbiturates, sodium amytal, Stroganoff therapy. (3) *Supportive measures:* Camphor and oil, intravenous saline, intravenous glucose (10%), digitalis, caffein, etc. (4) *Reduction of intracranial pressure:* Spinal or cisternal puncture, venesection, 50 cc. of 50% glucose in saline intravenously and decompression. No emphasis, however, has been placed upon the active dehydration measures. In 1920, Ravaut<sup>177</sup> called attention to the usefulness of sodium thiosulphate in a number of metallic poisons, such as arsenic, mercury, lead, bismuth, zinc and copper, as well as the sequelæ of arsphenamin. Busman and Woodburn,<sup>183</sup> McBride and Dennie<sup>184</sup> reported additional cases wherein it has been used. Stokes<sup>170</sup> advocates its use. This substance is one of a group of sulphur-containing salts and exerts a favorable influence by reduction of the metallic poisons to their non-toxic sulphids, and thus stops the toxic action and aids elimination. Marples and Myers<sup>185</sup> believe that the effect of sodium thiosulphate in these cases is due to the stimulation of that mechanism which normally takes care of the elimination of arsphenamin. They believe that the release of heavy metals from protein combination following sodium thiosulphate administration is rapid, and that they are liberated by the formation of heavy metal salts of thiosulphuric acid. Calcium thiosulphate has been used for postarsenobenzol complications.<sup>186</sup> The dose recommended is 5 cc. of a 10% solution daily for 3 days, and subsequently 2 and 3 times a week. Calcium chlorid has been used for the prevention of certain cutaneous inflammations by Chiari and Januschke,<sup>187</sup> in 1911, Blum,<sup>188</sup> in 1921. On theoretical grounds the combination of calcium and thiosulphate should be advantageous, particularly in those groups where sodium thiosulphate has failed. Solomon<sup>189</sup> found calcium chlorid was useful in the prevention of nitritoid reactions. Stokes<sup>200</sup> thinks that the detoxifying and irritation-reducing effect of calcium can be accomplished by using 10 cc. of calcium gluconate intravenously or intramuscularly just before the arsphenamin injection. This has seemed to smooth the course of some otherwise exceedingly reactive patients. Lipskeroff and Grebin, following the methods of Oliver, Yamada and Kulos,<sup>191</sup> tried blood serum and water diluent for neoarsphenamin, and found that it did not reduce toxicity. The use of water with calcium chlorid added<sup>192,193</sup> was found less toxic. This was corroborated by Lewin by using glucose solution as suggested by

Weitgassen,<sup>194</sup> and a marked reduction of toxicity was found. This reduction of toxicity by the use of glucose solution has been noted by numerous other authors.

In the 5 cases of myelitis, no attempts have been made to carry out the Queckenstedt test, as at the time of these case reports this newer method of diagnosis was unknown. In the case of encephalomyelitis under our observation the Queckenstedt test revealed a definite block. Furthermore, xanthochromic fluid was present, further verifying the presence of block. The rationale of laminectomy in such cases is borne out by the experimental work of Allen,<sup>195</sup> who indicated that in dogs a cord edema following trauma reached its maximum pressure within 4 hours. McVeigh<sup>196</sup> believed that the cord edema reached its maximum within 8 hours. It was the belief of Allen that this swelling of the cord, secondary to edema caused the nerve damage, and for this reason he recommended early laminectomy with longitudinal slitting of the cord. In these cases the edema occurs before the hemorrhagic process develops and such therapy is definitely indicated. Coleman,<sup>197</sup> in cases of spinal cord trauma, has advised the use of the Queckenstedt test to determine the presence of spinal block. This test is carried out by performing a spinal puncture and compressing the jugular vein. The rapidity of the rise and fall of the spinal fluid in a water manometer indicates the presence or absence of block (Stookey and Klenke<sup>198</sup>). Naffziger<sup>199</sup> believes that the traumatic cases should be placed in the category of an early emergency operation, and agrees with Coleman in advising early laminectomy, particularly when the fluid does not rise at all in the spinal manometer by jugular compression. In view of the serious outcome of these cases, it is our opinion that the Queckenstedt test should be performed daily to determine whether a block is present and, should any evidence of block occur, we advise a decompressive laminectomy at the level of the lesion. It is our belief that dehydration measures are actively indicated in these cases, and that the acute brain and cord edema that arises plays an active part in the final outcome of the case. An acute brain edema with rise of intracranial pressure is part of this picture and has been previously called to our attention by Ehrlich,<sup>23</sup> Hammer,<sup>36</sup> and also by Stuhmer<sup>98</sup> who in the early days recognized its importance and advised decompression. Eight cases that came to autopsy showed brain edema and hyperemia without hemorrhage. Furthermore, in the 39 cases that had lumbar puncture, 25 showed evidence of increased intracranial pressure. For dehydration measures, we advise the use of 50 to 100 cc. of 50% glucose solution intravenously every 3 to 4 hours; retention enemas consisting of 6 ounces of magnesium sulphate crystals dissolved in 4 ounces of water. Should the pulse become too rapid glucose may be given in less frequent amounts, and normal salt be given intravenously. If these measures prove of no avail, lumbar puncture may be performed repeatedly with the removal of 25 to

50 cc. of fluid. Judgment must be exerted during the course of the disease as to the limitation of fluid intake. In some cases this is advisable, in other cases undesirable. If brain edema continues to increase with its resulting rise of intracranial pressure, subtemporal decompression with drainage of the subarachnoid space should immediately be carried out. Subtemporal decompression has been performed in 3 patients.<sup>2,12,98</sup> In 1 the brain appeared normal, and in 2 the brain and meninges were edematous. All of these patients, however, succumbed to the procedure.

**Conclusions.** 1. The mortality of cases with central nervous system involvement secondary to intravenous injection of arsphenamin is about 76%.

2. There is approximately 1 death due to central nervous system involvement in every 5398 cases treated, and in every 28,768 injections.

3. The term, "hemorrhagic encephalitis," is not adequately descriptive.

4. The toxic reaction may occur in non-luetic cases, is not related to the quantity of the drug given, nor the number of injections, nor the toxicity of the drug itself. It is not related to the age of the patient nor the sex. It occurs most frequently after the 2d dose, though it has been reported as occurring after the 15th dose. Furthermore, cases have been reported where the drug has not at first produced toxic effects, but when again given several years later toxic reactions resulted. The symptoms may occur from 12 hours to 70 days after the injection, but usually develop from 12 to 144 hours.

5. The outstanding symptoms are headache, vomiting, nervousness, chills and dizziness, with physical signs of fever, cyanosis, respiratory and pulse changes. The outstanding neurologic signs are convulsions, unconsciousness, pupillary and ocular muscle changes, reflex changes, loss of sphincter control, mental disturbances, hemiparesis and rigidity of the neck. Laboratory reports indicate the presence of an acute nephritis in a relatively large percentage of the cases as well as an increased spinal fluid pressure.

6. Myelitis and encephalomyelitis may also occur, while meningitis may coëxist.

7. This toxic reaction is diffuse rather than focal, as pathologic reports and clinical findings indicate involvement of the other organs. The clinical diagnosis is derived from the organ indicating the greatest involvement, *e. g.*, if the brain shows predominating clinical signs, it is an encephalitis; if it is the cord, it is myelitis; if the liver, a hepatitis.

8. The methods of therapy have been described in detail and consist primarily of prophylactic and curative measures. The curative measures are detoxification and reduction of intracranial pressure by medical or surgical methods. Sedatives and supportive measures should be utilized.

## SPONTANEOUS RUPTURE OF THE ESOPHAGUS IN SYPHILIS.

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MANY physicians believe that the esophagus is relatively immune to pathologic processes, and that, barring congenital defects, trauma, cardiospasm, constrictions, varices, benign and malignant neoplasms, it may be disregarded as a seat of disease. Mosher,<sup>1,2,3</sup> however, in the largest reported series of postmortem specimens studied has conclusively shown that the esophagus is much more vulnerable to every type of lesion than has heretofore been the popular belief. In one series of 100 consecutive organs obtained from routine autopsies he found pathologic lesions in 14 specimens. These were septic emboli, acute and chronic inflammations, degenerations, benign tumors and the like. His studies emphasize the need for a more careful study of this organ in the routine autopsy.

Spontaneous, non-traumatic, complete rupture of the esophagus is a rare condition, if the number of reported cases in the literature is any criterion. Gott<sup>4</sup> as a result of such a survey on the subject discovered only 38 such cases, the first being the celebrated one of the Baron Wassenau in 1724. Gott added 4 cases, 2 of which were due to multiple bacterial emboli occluding the esophageal capillaries in patients with meningococcic meningitis. He concluded that cardiospasm, stricture, ulcerations, esophagitis and vascular changes in the esophageal wall predispose to rupture.

Mallory and Weiss<sup>5</sup> observed 15 patients who, after long alcoholic debauches, developed massive hematemesis. They reported the postmortem findings in 4, all of whom showed lacerated but not ruptured lesions of the cardia of the esophagus. As none showed any evidence of liver cirrhosis it was concluded that the hematemesis was not from ruptured varices due to liver cirrhosis. They suggested that the lacerations may have been produced by pressure changes in the stomach during retching, vomiting and regurgitation. They felt that such lesions could develop in other conditions in which severe retching and vomiting occurred, such as in pernicious vomiting of pregnancy and neoplasms. In a later report<sup>6</sup> these authors presented 2 more instances of lacerated esophagi in patients—also alcoholics—both of whom died and the autopsies revealed lacerations through the esophageal mucosa. Gott agreed with them

that the inciting cause of either laceration or rupture of the esophagus was sudden, increased, intra-esophageal pressure.

There has not been found any reported cases of rupture of the esophagus due to luetic periarteritis of the esophageal wall. Luetic periarteritis leads to ischemia of the part supplied by the artery with subsequent arterial occlusion by scar formation. This scarring materially weakens the wall the extent of which is dependent upon the size of the scar. If the scar includes a portion of the lining mucosa, the autolytic enzymes from regurgitated gastric contents would have a vulnerable point of attack which could more easily erode the wall. Such a sequence of events would be a combination of etiological factors expressed by Mosher, Gott and Mallory and Weiss as tending to enhance the possibility of laceration or rupture.

In syphilitic patients, any organ or combination of organs including the esophagus may be affected by the disease. Then, too, in those patients with central nervous system involvement, retching and vomiting occasionally occur. The combination of esophageal periarteritis and severe retching and vomiting (during "paretic seizures") should offer rather good possibilities of either lacerations or ruptures of the esophagus. In spite of this, apparently the incidence of such occurrence in the literature is *nil*. It is our feeling, however, that this may be due, in part at least, to the fact that the esophagus is generally disregarded in the routine postmortem examination. In our own institution, in the last 436 consecutive autopsies performed, 44 were on patients with syphilitic central nervous system involvement. Of these, only 5 died during "paretic seizures." Of these latter, 2 patients died of hemorrhage resulting from complete, non-traumatic rupture of the esophageal wall. In no instance were lacerations without complete rupture found. The following case record abstracts are from the records of these 2 patients.

**Case Abstracts.** CASE 1.—A. R. (No. 38909), a white girl, aged 12, a congenital luetic diagnosed as having juvenile paresis, was admitted to the Worcester State Hospital in 1929 having received specific treatment for several years before admission. Her subsequent study revealed a rather typical clinical and laboratory picture of juvenile paresis for which she received malaria, bismuth and sulpharsphenamins. She eventually had repeated paretic seizures which lapsed into status epilepticus. On the 3d day prior to death (1932, age 15) she had a maximum number of daily seizures which reached 50. The rectal temperature rose rapidly to 106, pulse fluctuated between 130 and 140 and respirations from 30 to 50. Her pupils were unequal and irregular and reacted sluggishly to light. There were impaired resonance and increased breath sounds and râles at both bases. The blood pressure was 90/70. All of the peripheral nerve reflexes reacted sluggishly to stimulation. No patellar reflexes were elicited. Babinski reflexes were obtained on both sides. She was semicomatose for 3 days and died suddenly.

**AUTOPSY.** (2.3 hours after death.) No evidence of postmortem degeneration. The patient was found to have died of complete rupture of the esophagus. The posterior mediastinal space contained approximately 100 cc. of a thin, "coffee-ground," black colored material, undoubtedly



gastric and esophageal contents. In the left lateral wall of the esophagus was a longitudinal rent measuring 3.1 cm. long, the caudal end of which was 2.3 cm. above the cardia. The esophageal wall surrounding the rent was completely hemorrhagic and black. The edges of the rent showed, in addition to the massive hemorrhage, many esophageal vessels with a perivascular infiltration of lymphocytes, endothelial leukocytes, some plasma cells and fibroblasts. Complicating the picture were numerous pigment laden leukocytes and edema. Rare spirochetes were found by special staining methods.\* The other viscera were essentially normal.



FIG. 1.—Case 1. Esophagus showing longitudinal rent and hemorrhagic mucosa. The rectangle of tissue removed below the rent was taken for microscopic examination. Note the thinness of the wall and the absence of normal rugæ.

CASE 2.—C. E. (No. 36285), a white male, aged 49, was admitted to the Worcester State Hospital in 1925 with a diagnosis of "psychosis with cerebrospinal syphilis." His syphilitic condition had been treated with tryparsamid and bismuth. In 1930 he developed signs and symptoms of duodenal ulcer without complete obstruction, confirmed by laboratory and Roentgen ray findings. For the last 1½ years he had had parietic seizures. On July 10, 1932, he rapidly became jaundiced, the abdomen became distended and the liver edge was felt 2 cm. below the costal margin. Ascites developed with shifting abdominal dullness. His icterus intensified. He began to vomit and have hiccoughs. On July 15, he had occult blood present in vomitus for the first time, gradually became comatose and expired (5 days after the onset of jaundice). His temperature, pulse and respirations remained normal to the end.

AUTOPSY. (2 hours after death.) Showed that the patient died of complete rupture of the esophagus with hemorrhage. Figures 2 and 3 give an idea of the extensive hemorrhage in the wall of the ulcer itself. The rent was 3 cm. in length, the caudal end of which was 1.5 cm. above the esophageal gastric junction. The posterior mediastinal space contained about 75 cc. of a thick, mucoid, "coffee-ground" colored fluid. In the histological study of this specimen the hemorrhage was so extensive as to almost obliterate the histological architecture of the wall surrounding the rupture. In

\* The type of stain used for spirochetes is a modified silver stain after De Galantha (Am. J. Clin. Path., 2, 63, 1932).

addition, this patient had an atrophic cirrhosis of the liver (weight 940 gm.), almost simulating a "classical Hepar Lobatum," with ascites and jaundice. The remaining viscera showed lesions consistent with his age and relatively irrelevant.



FIG. 2.—Case 2. The unopened esophagus showing the complete rupture near the cardiac orifices. A white glass rod is in the lumen of the esophagus. Note the markedly hemorrhagic wall.

**Discussion.** In the first case, it is demonstrated that syphilis caused the periarteritis in the esophageal wall. It is logical to assume that these lesions materially weakened the wall. Attacks

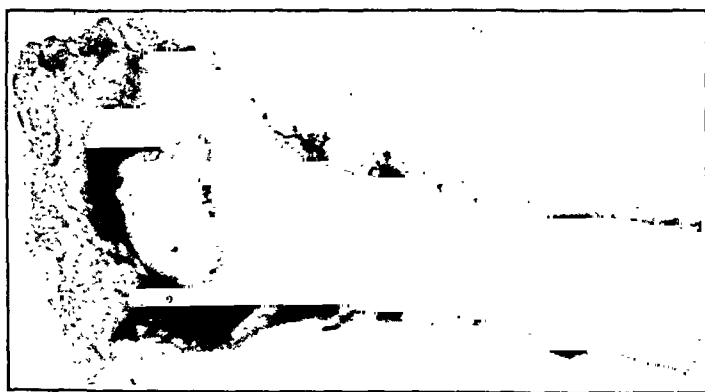


FIG. 3.—Case 2. Same specimen as in Fig. 2 after opening. Note the markedly hemorrhagic mucosa and complete absence of the normal rugæ. Note the large crater-like area surrounding the hole of the rupture. In this specimen, only the proximal 2.3 cm. of the esophageal wall was normal.

of retching such as are present in paretic seizures cause extremes of intra-abdominal pressure which are easily transmitted through the diaphragm to the wall of the esophagus. The regurgitation of autolytic gastric contents over the lining of the esophagus which

has been already damaged by the luetic reaction tends to erode it, allowing these contents to come in contact with the muscular layers.

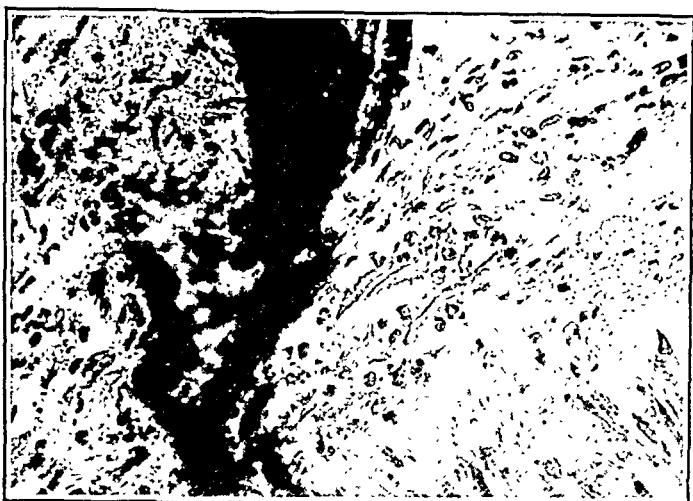


FIG. 4.—Case 1. Microphotograph of luetic perivascular infiltration of lymphocytes and endothelials, with occlusion and scar formation in the wall of the esophagus, near the area of eruption. Note large hemorrhagic areas in the scarred wall. Magnified 400 X. (Due to the large amount of blood pigment the spirochetes photographed too poorly for reproduction.)

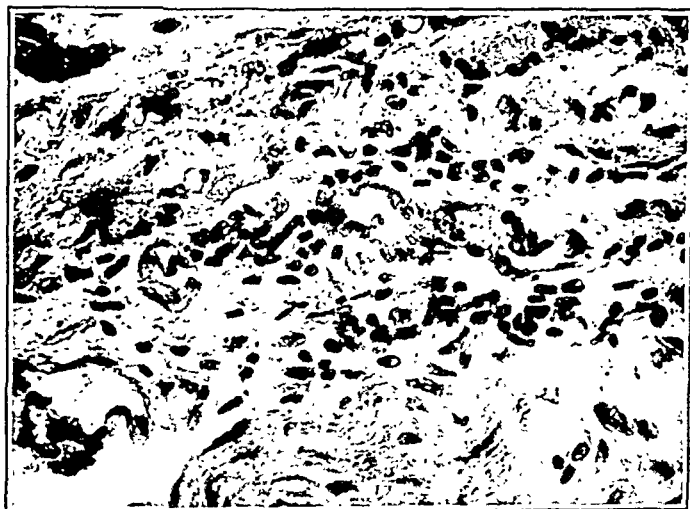


FIG. 5.—Case 1. Microphotograph of section of the esophageal wall, showing hyperplasia of the endothelials with perivascular infiltration of fibroblasts and lymphocytes, with partial occlusion of one vessel. Magnified 400 X.

To substantiate this hypothesis, the epithelial lining around the rent in both specimens was almost completely denuded. We have, therefore, in both instances a weakened esophageal wall being

acted upon by autolytic enzymes and severe intra-abdominal pressure, forming an ideal point of rupture.

In 496 consecutive autopsies performed on mentally ill patients, 5 were found to have died during a paretic seizure and of these latter, 2 (40%) died of a sudden complete rupture of the esophagus. Although the actual number of those dying in paretic seizures is small and percentages drawn from such a small sample are wholly inadequate, yet the relatively large number (40%) of those dying of rupture of the esophagus shows the tendency of such occurring more frequently than the literature would lead one to suppose.

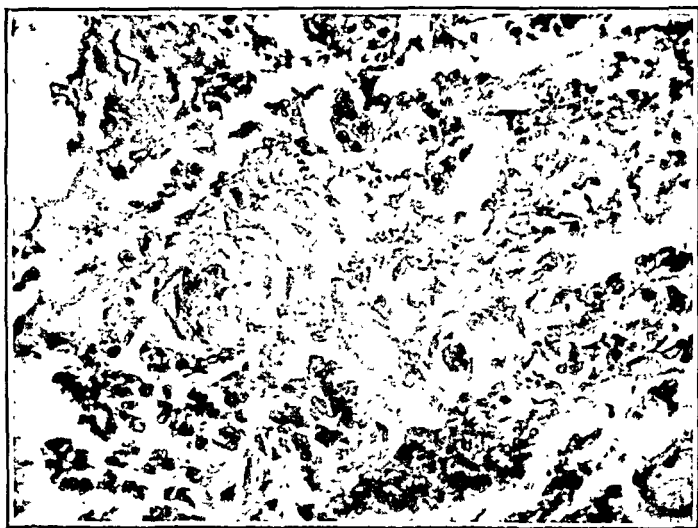


FIG. 6.—Case 2. Perivascular infiltration and occlusion deep in the wall of the esophagus. Note the large scarred area in the center of the picture. Magnified 400 X.

**Summary.** Syphilitic periarteritis of the esophageal wall usually leads to vascular occlusions, scar formation and damage to the epithelial lining at those points. Luetic patients in whom the central nervous system has been involved in the disease process may have attacks of the so-called "paretic seizures" of which retching and vomiting are prominent features. The combination of the esophageal scars, sudden extremes of intra-abdominal pressure and the autolytic action of the regurgitated enzymes of the gastric contents may result, in rare instances, in sudden rupture of the esophageal wall.

Two case reports are presented, both on patients who died from sudden, complete rupture of the esophageal wall. One was a 15-year-old congenital luetic with the juvenile form of general paresis. The second case was that of a 58-year-old patient suffering from acquired lues with central nervous system involvement. Each died during an attack of "paretic seizures."

**Conclusions.** Complete rupture of the esophageal wall may occur, in relatively rare instances, due to syphilitic periarteritis of the organ and severe retching and vomiting which is a rather common accompaniment of parietic seizures.

A routine, detailed examination of this organ in all autopsies is urged.

The esophagus is more vulnerable to pathologic lesions than the statistics have heretofore indicated.

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## OBESITY TREATMENT BY DIET, THYROID AND DINITROPHENOL.

### RESULT ON 106 OUTPATIENTS.\*

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SINCE 1930, patients complaining of obesity have been referred to the Endocrine Clinic for systematic treatment. Diet and thyroid carefully dosed have been our mainstays, and some other glandular extracts have been tried. While an analysis of the material was in progress, Prof. Tainter suggested, in the fall of 1932, that dinitrophenol might be useful in the treatment of obesity, and with his associates has published exhaustive metabolic studies of its pharmacologic effects in both animals and man, including the obese. The drug was, therefore, added to the methods which were already being surveyed under the far from ideal but fairly uniform conditions of outpatient care.

**Material.** The records of some 200 obese patients who attended the Endocrine Clinic during the period between January, 1931, and May, 1933, were sifted. Growing children were excluded, so that all patients were

\* Aided by the Rockefeller Fluid Research Fund.

adults, except for 3 girls between 16 and 17 years whose records showed no growth at time of treatment. Complicating disease was taken as cause for exclusion only where it seemed likely to induce weight changes, as, for instance, heart failure with edema or uncontrolled diabetes mellitus.

Concerning attendance and coöperation, no very rigid standard was set up. All those included had attended clinic at least 3 times, with an interval of at least 30 days between the first and last visits. They had kept their appointments with fair regularity, and made a reasonable attempt to follow advice. In some patients coöperation varied, being good in some periods and obviously bad in others, so that the latter periods were discarded. The main difficulty in securing coöperation, of course, was in regard to diet; there was never an objection to taking oral medicine. No records were disqualified because the weight loss was disappointing.

The residuum consists of records of 104 women and 2 men. All were white except 2 women.

**Therapeutic Procedure.** Patients came to this special clinic only after a history had been taken and a physical examination done in the medical clinic. Laboratory work included urinalysis and basal metabolism on all patients, and blood sugar or sugar tolerance tests and Roentgen rays of the sella where indicated. The net height was determined at the first visit, and records of net weight (by subtraction of 3 to 5 pounds for women's clothing and 6 to 8 pounds for men's, as seemed appropriate) made at every visit.

At the first visit each patient was given a copy of a reducing diet, containing 80 gm. of carbohydrate, 60 gm. of protein and 40 gm. of fat, giving a total of 920 calories, outlined in grams and household measures, to show the exact food distribution recommended for 3 meals a day. It had provision for vitamins and salts. The patient was asked to approach the prescription as closely as possible, and to bring an estimate in ounces or tablespoonfuls of the food eaten the day before attendance; this actual list was then calculated at each visit.

Patients were kept on this simple dietary régime so long as the loss was satisfactory, *i. e.*, at least 2 pounds per month, continued moderate loss being preferred to more dramatic reductions. Many patients reached their ideal weight by dieting only. In general, drugs were added when the patient's weight had been stationary for 2 visits. They were tried in turn and singly, each new régime being maintained so long as it was effective or until it was shown to be ineffective. Continuance of diet was insisted on. No effort was made to control the water metabolism in this series.

In making the analysis, each type of treatment, *i. e.*, diet alone, diet plus thyroid and diet plus dinitrophenol, was considered as a separate period. The various preparations other than thyroid and dinitrophenol used during the study are not presented here.

*Diet Alone.* One hundred patients were on a period of dietary régime before medication; 72 of the 100 became stationary in less than 4 months; the remaining 28 were on diet for periods of 4 months to 1 year or more.

*Diet Plus Thyroid.* This group included 51 patients. The dose was 1 grain daily of desiccated thyroid (Armour) for a week, then gradual increase to tolerance. This was measured, not by basal rates (too expensive), but by too rapid pulse, nervousness, headache or other discomfort. The pulse as taken at the clinic was not allowed to go above 100. The maximum daily dose usually turned out to be 2 or 3 grains, and the average dose was  $1\frac{1}{2}$  grains.

Of the 51 patients, 41 were given thyroid after they were stationary on diet alone, 6 simultaneously with diet (on account of symptoms of hypothyroidism) and 4 after dinitrophenol.

*Diet Plus Dinitrophenol.* This group included 23 patients. The drug was given and dosage controlled just as for thyroid, according to clinical indications and not by basal metabolic rates. The drug was put up in 75-mg. capsules or, more recently, in equivalent 100-mg. capsules of sodium dinitrophenol. Patients were first tried on 1 capsule daily for 1 week before the dose was gradually brought up to tolerance. The maximum daily dose in this series was 300 mg., and the average daily dose was 165 mg. It was taken all in 1 dose, with at least 250 cc. of water to follow, thus avoiding any epigastric discomfort after swallowing; and usually in the evening, so that the flushing and heat which occur particularly a few hours after administration should come on in bed. No more than a week's supply was given, and every patient was sharply warned against taking any more than the daily ration prescribed.

**Analysis of Data.** For every type of treatment the *means* were calculated for the following: age, basal metabolic rate and weight at beginning of treatment; daily caloric intake and dosage during treatment; length of period and weight loss before treatment; and number of days and weight loss on treatment.

The *time factor* in treatment proved a difficult one to evaluate because the length of time between visits and consequently the lag in the manipulation of treatment depended much more on the convenience of the patient than on the demands of good practice. Consequently, the total average weight loss on any particular régime which was maintained so long as it was effective, seemed a better measure of effectiveness than a rate of loss. Nevertheless, the durations of treatment were calculated, and where they seem to be significant will be mentioned. In a future analysis, when more evidence is at hand, the study of the rate of loss in pounds per day is expected to be profitable.

*Periods* longer than 1 year represent largely the records of patients who had been on a self-imposed effective home diet before enrolling in the clinic, and whose records were extended backward retroactively to include their preliminary efforts. Their records are in every case pooled with the 1-year periods.

**Results.** *Diet alone* took off approximately 15 pounds in about  $3\frac{1}{2}$  months, and thereafter not much more (until medication was

added). About 1 in 4 patients, however, lost as much as 20 pounds in this time, achieving finally about 30 pounds' total loss, with an occasional patient losing as much as 60 pounds. It was often not clear why some patients succeeded so much better than others, but in general weight loss was related to original weight, basal metabolism and duration of treatment. Specifically, weight loss and original weight showed a slight positive correlation ( $r = 0.33 \pm 0.06$ ), *i. e.*, the heaviest patients tended to lose the most. Also, when the basal metabolism was normal the patients lost better than when it was depressed ( $r = 0.24 \pm 0.07$ ). The time on treatment is likewise related, although it is too variable a factor to warrant converting the figures into rates of loss.

Patients' reports of diet were apparently inaccurate. Although reports varied between 400 and 1600 calories, the weight loss varied with the reported caloric intake only in that the loss was less where the diet was admittedly above 1200 calories. Age also appeared to be a negligible factor in the present study.

Based on the above considerations, thyroid and dinitrophenol may now be discussed.

*Diet Plus Thyroid or Dinitrophenol.* When patients had become stationary on diet alone, roughly after 10 to 20 pounds had been lost, it was possible to induce a further loss of about 12 pounds with either thyroid or dinitrophenol. Specifically, this further loss averaged 11 pounds for 41 patients on thyroid *versus* 12 pounds for 13 patients on dinitrophenol. When the basal rate was low, both drugs appeared to be more effective than when it was normal, but the number of patients was too small to prove this. Where the basal metabolism was normal (above  $-5\%$ ), the dinitrophenol appeared to be more effective than the thyroid: in pounds' loss,  $12.67 \pm 1.47$  (average of 9 patients) against  $7.38 \pm 1.58$  (average of 16 patients). This dinitrophenol loss was accomplished in 51 days and the thyroid loss in 93.

It must be emphasized that, even here, where the weight loss is almost twice as great on one treatment as on the other, the figures do *not* prove to be statistically significant on account of the limited numbers and wide distribution of results. This is true of all the figures reported in this paper (and, in fact, in many clinical papers).

Nevertheless, the results of the study do show consistent tendencies which appear to be worth presenting, and which deserve to be extended into studies on larger series.

*Thyroid Dinitrophenol Switch and Vice Versa.* After patients had become stationary on diet alone followed by the addition of either thyroid or dinitrophenol, *i. e.*, after about 20 pounds were lost, another 4 pounds' loss was forced by switching from thyroid to dinitrophenol (average of 6 patients), and also 4 pounds (average of 4 patients) by switching from dinitrophenol to thyroid. Since neither drug was notably effective in second place, this may mean



that, although on dinitrophenol patients apparently lose faster, they do not, on the average, lose more. This is a point which we particularly wish to investigate further.

Three groups which do not fit into the above classification are considered next.

*Thyroid Instituted Immediately.* Six cases in which thyroid was given immediately, along with diet, lost an average of 22 pounds, which is essentially the same as the loss shown by those patients who were given diet first and thyroid later. The time of treatment was around 7 months in both instances. This fact permits the conclusion that there is no advantage in starting medication until diet alone has accomplished all it can.

*Dinitrophenol Without Diet.* Separately considered are the 3 patients who failed to restrict their diets while on dinitrophenol. Their loss was *nil* (gained 1 pound, gained 8 pounds and lost 9 pounds respectively) during an average period of 62 days and on an average daily dosage of 200 mg. These 3 patients are of more interest than the usual cases of overeating because they had always been uncoöperative and were chosen for just that reason in order to see whether weight loss could be forced, even on an unrestricted diet. No final conclusions are justified from 3 cases, but it would seem probable that, at least on moderate dosage of dinitrophenol, no weight loss is to be expected unless the patient is likewise restricting his caloric intake.

*Side Effects of Dinitrophenol.* Ill effects were noticed in 3 cases: 1 patient reported nausea after the first few doses and did not continue with it; another finally stopped because she complained that she was "burning up;" a third patient was getting good results but was taken off the medicine after 7 days because she appeared somewhat jaundiced, a phenomenon which is now known to be due, not to liver damage, but to the coloring of the serum by the dinitrophenol itself. Other patients were able to continue with no unfavorable symptoms except flushing, occasional night sweats and subjective feeling of heat.

**Summary.** The methods used in treating 106 unselected obese patients in the outpatient clinic were analyzed, with reference to the effects of diet alone (100 cases), thyroid (51) and dinitrophenol (23).

The weight losses shown here are not so great with any of these methods as could have been achieved if patients had restricted their diets more conscientiously. They do, however, represent the sort of results which may be expected in outpatient care of unselected patients, and, therefore, permit the following tentative practical conclusions:

1. Diet alone will take off an average of 15 pounds in  $3\frac{1}{2}$  months and, therefore, should be the first therapeutic procedure in the treatment of obesity.

2. When dieting fails to get results, either thyroid or dinitrophenol appears to be an effective adjunct.

3. As an adjunct to diet, dinitrophenol is at least as effective as thyroid and, in patients with normal basal metabolism, possibly superior.

4. Thyroid given immediately with the beginning of diet caused no better weight loss than when it was given only after loss on diet had stopped.

5. Dietary control was necessary to achieving results with dinitrophenol, as it was to getting results with thyroid. Furthermore, reasoning from the thyroid results by analogy, it would seem that it is worth while removing as many pounds as possible on diet alone before exhibiting the dinitrophenol—this on the assumption that with any drug which is not compensating a physiological deficiency, the less given, the better for the ultimate health of the patient.

6. It should be emphasized that neither thyroid nor dinitrophenol should be used indiscriminately by patients unguided or under the direction of physicians inexperienced with their use.

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### A PRELIMINARY REPORT ON THE CLINICAL APPLICATION OF A POLYVALENT STAPHYLOCOCCUS BACTERIOPHAGE IN BRONCHOSCOPY.

BY WILLIAM FREDERIC MOORE, M.D.,

AND

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EIGHT years ago we attempted similar experiments in this clinic. At that time an autogenous polyvalent phage was developed by Dr. G. R. Moffitt. The attempt to make this practically available was abandoned for three reasons, namely: (1) the expense attached to its development in each individual case; (2) the elapsed time before the phage was available for injection; (3) the product proved extremely unstable.

A commercial bacteriophage, with a mercurial salt preservative, was used for a 3-month period in this clinic. The results of this therapeutic agent have been variable. On the basis of such varia-

bility this commercial bacteriophage was tested for its living and active properties. It was contacted against several stock strains of staphylococcus with a yeast extract broth (Savita) as a medium.<sup>1</sup> A "Cross-test" was performed with the above stock strains and the commercial bacteriophage by plating the young sensitive stock strains on a yeast extract and 1% agar plate and then touching this inoculation with a small needle loop full of bacteriophage. The commercial bacteriophage did not show lysis or produce a "clearing" with the stock strains of bacteria. With these two negative tests, and on the basis of Rakietsen's work it was assumed that the bacteriophage had been destroyed by the mercurial salt present in the preparation. The phage used had about one-half the quantity of mercurial salt as that supplied to the profession.

An active polyvalent bacteriophage for staphylococci and streptococci has been prepared and is now used in the clinic. Several stock strains of staphylococci and streptococci were contacted to three polyvalent staphylococcus and streptococcus strains of bacteriophage.<sup>3</sup> Young sensitive stock strains of the above bacteria (18 to 24 hours), in a Savita-broth medium, were contacted to the stock bacteriophage. This bacteriophage-bacteria mixture was incubated for 24 hours at 37° C. and examined for lysis. Lysis was found to be complete and the control tubes checked this reading. In conjunction a "Cross-test" was made, using the same strains of bacteria and bacteriophage; all bacteriophage strains were found active on reading the agar-Savita plate after 24 hours of incubation at 37° C.

The tubes of bacteriophage-bacteria showing lysis after 24 hours were filtered through Chamberland filters ( $L_5$ ). The filters were prepared prior to each filtration by subjecting them to muffled heat up to a red glow, cooling, packing and autoclaving for 30 minutes at 15 pounds pressure. A specimen of this bacteriophage filtrate was plated on Savita agar and tested for sterility. The filtrate was ampuled in 5 cc. sterile vials, closed by flame, and put in an incubator at 56° C. for 1 hour, for 3 different times. A final turbidity "Tyndall Effect" reading was made on the filled ampules; some of the filtrate also remained at room temperature, approximately 20° C., for several days and was read for turbidity.

Twenty-eight patients were treated, including 14 with bronchiectasis, 10 with lung abscess and 3 with chronic bronchitis. Of 10 in whom the commercial bacteriophage was used, 4 showed improvement; 6 showed no improvement, either clinically or symptomatically, and 1 died of an intercurrent pulmonary hemorrhage. Eighteen patients were treated with the special bacteriophage prepared for this clinic. All but one showed decided improvement after 2 or more instillations. Two were discharged from the clinic apparently cured.



FIG. 1.—Case 15, Table 2, lung abscess, bronchiectasis, both lobes left side.

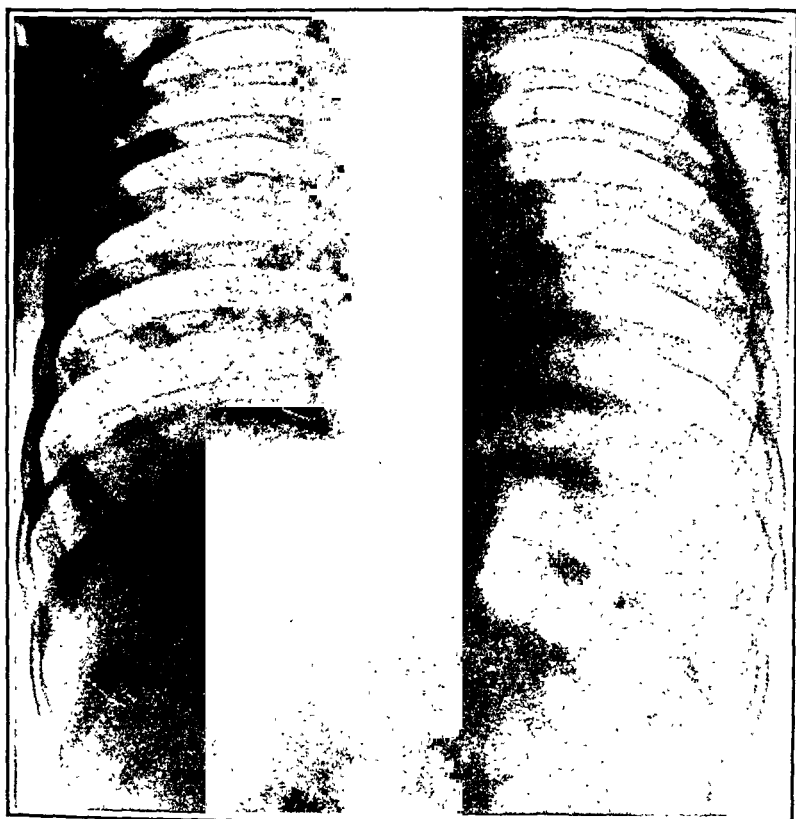


FIG. 2.—Case 15, Table 2, after two instillations of bacteriophage.



TABLE 1.—RESULTS IN 10 PATIENTS TREATED WITH A COMMERCIAL BACTERIOPHAGE.\*

Cases.	Diagnosis.	Laboratory findings.	No. of treatments.	Improved.	Unimproved.
1. J. S.	Bronchiectasis	Strep. viridans; pneumococcus	3	+	
2. J. T.	Bronchiectasis	Strep. viridans; pneumococcus	3		+
3. F. A.	Bronchiectasis and lung abscess	Pneumococcus, strep., M. catarrh., and H. influenzae	1		+
4. R. B.	Bronchiectasis	Pf. bac., pneum., strep., M. catarrh., non-hem. strep., diphtheroids	2		+
5. I. B.	Bronchiectasis	No specimen	5	+	
6. P. H.	Bronchiectasis	Strep. viridans, staph. albus	1	+	
7. J. R.	Bronchiectasis	Pneumococcus, hemolytic staph. albus	5	+	
8. O. S.	Bronchiectasis	No specimen	2	(Died pul. hem.)	+
9. K. A.	Empyema	Overgrown with B. subtilis	1		+
10. M. B.	Lung abscess, extensive involvement	No specimen	1		(Died) +

\* Commercial bacteriophage with the addition of a mercurial salt.

*Technique.* Patients were treated at 7-day intervals, except during a 2-week period, when the phage was not available. All cases of pulmonary suppuration were treated, with the exception of those with a bronchoscopically evident bronchial asthma considered to be of extrinsic origin. The technique was the same as that used in the bronchoscopic treatment of any pulmonary suppuration. The draining bronchus or bronchi were localized; any impediment to free drainage was removed either at once or gradually and the secretion present thoroughly aspirated. A specimen was taken directly from the bronchus in a special collection tube for laboratory examination and culture, insuring against contamination by buccal or throat secretions. Five cubic centimeters of the bacteriophage were then injected directly into the bronchus, previously cleared by aspiration. An attempt was made to have this retained by instructing the patient to check the cough as long as possible.

*Observation.* Adequate and continued drainage is the bronchoscopist's chief aim in dealing with pulmonary suppuration. Thick, viscid secretions undoubtedly impede ciliary action<sup>4</sup> and may partially or completely obstruct a draining bronchus. It was therefore noteworthy at subsequent bronchoscopies after the use of our bacteriophage that the secretion was both less in quantity and altered in quality, the secretion becoming much thinner and the

odor markedly less. One patient with illness of 4 years' duration received regular bronchoscopic treatments for the last 2 years, including also injections of the commercial stock phage, without much benefit. In the past 3 months, since receiving our special bacteriophage, she has progressed remarkably, with improvement, as evidenced by lessened productive cough, after the first instillation.

TABLE 2.—RESULTS IN 18 PATIENTS TREATED WITH A SPECIAL POLYVALENT STAPHYLOCOCCUS BACTERIOPHAGE DEVELOPED AT THE PHILADELPHIA GENERAL HOSPITAL.

Cases.	Diagnosis.	Laboratory findings.	No. of treatments.	Improved.	Unimproved.
1. W. Mc.	Lung abscess	Overgrown with <i>B. proteus</i>	2	+	(Died) +
2. J. K.	Lung abscess	<i>Strep. viridans</i> , <i>Staph. albus</i>	4		
3. T. R.	Lung abscess	<i>Pneumococcus</i>	12	+	
4. J. RO.	Lung abscess	Myriads of hemolytic strep. and <i>B. influenzae</i>	4	+	
5. E. W.	Lung abscess	<i>Strep. viridans</i> , <i>pneumococcus</i>	4	+	
6. W. L.	Chr. bronchitis	No specimen	3	+	
7. M. M.	Chr. bronchitis (rt.)	<i>Strep. viridans</i> , <i>Staph. albus</i>	4	+	
8. M. L.	Pulm. suppuration (rt.)	Gauze packing; no growth	4	+	
9. W. H.	Tracheal bronchitis	<i>Strep. viridans</i> , <i>M. catarrh.</i> , <i>H. influenzae</i>	3	+	
10. E. H.	Tracheal bronchitis	<i>Strep. viridans</i> and non-hemol. strep., <i>Staph. albus</i> , diphtheroids	2	+	
11. J. T.	Pulm. suppuration (lt.)	No specimen	4	+	
12. L. S.	Pulm. abscess (rt. low.)	<i>Strep. viridans</i> , hemolytic strep. and <i>H. influenzae</i> , <i>Staph. albus</i>	2	+	
13. M. R.	Pulm. abscess (lt. low.)	No specimen	2	+	
14. A. R.	Bronchiectasis	No specimen	4	+	
15. F. A.	Bronchiectasis and lung abscess	No specimen	2	+	
16. M. O.	Bronchiectasis	<i>Strep. viridans</i> , <i>pneumococcus</i>	5	+	
17. W.	Bronchiectasis	No report	3	+	
18. M. Mc.	Bronchiectasis	<i>Strep. viridans</i> , <i>pneumococcus</i>	3	+	

**Conclusion.** 1. An active polyvalent staphylococcus bacteriophage, such as prepared by us, is of apparent value when applied bronchoscopically in the treatment of bronchopulmonary suppuration.

2. Drainage is facilitated by its use, as it changes the character and quantity of the secretion.

3. This being a preliminary report, continued observations should be made to confirm the above findings.

Dr. Love wishes to express his appreciation for the association made with Professor Felix d'Herelle and Dr. Morris L. Rakieta while learning much of this technique. It was through the kindness of Prof. d'Herelle and Dr. Rakieta that he received the original stock strains of bacteriophage mentioned in this paper.

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### FOREIGN PROTEIN THERAPY.

#### I. HEMOCYTOLOGIC CHANGES FOLLOWING THE INTRAVENOUS INJECTION OF KILLED TYPHOID, PARATYPHOID "A" AND PARATYPHOID "B" BACILLI.

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THE changes in the cytology of the circulating blood due to the injection of foreign proteins into the circulation has received scant attention when one considers the vast amount of foreign protein therapy that is employed at the present time. With the development of our knowledge of the cytologic alterations of the blood it has become apparent that the reaction of a patient to an infection or to an intravenous injection of foreign protein is reflected in most instances by such cell changes.

**History.** For centuries it has been known those with chronic disease are occasionally benefited by an intercurrent acute infection. In more recent times it has been observed that such diseases as typhoid, typhus, cholera, smallpox, erysipelas and measles often left a patient suffering from a chronic luetic or tuberculous infection markedly improved. With this in mind, Fehleisen cultured streptococci from a case of erysipelas and then injected them locally in a patient with lupus. The results were remarkable in that the patient was apparently cured. In 1886, Emmerich cured a case of anthrax with a similar culture. Specific therapy, however,



occupied the foreground until Ichikawa, in 1914, found that patients suffering from paratyphoid fever responded to injections of killed typhoid bacilli as well as patients with typhoid fever. Vaccines from colon bacilli were used by Kraus and Mazza with success in cases of typhoid fever. Ludke, in 1915, demonstrated that the course and symptoms of typhoid fever could be aborted by the intravenous injection of proteose. Following the use of proteose, the term "protein therapy" was coined.

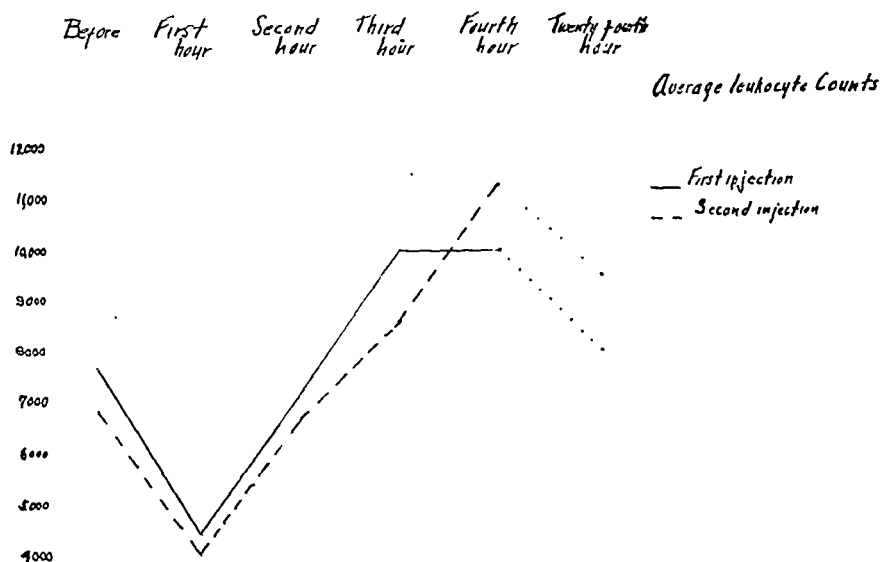
A number of references are found in the literature relative to the results obtained from the intravenous administration of foreign proteins. Whenever the investigators made examinations of the formed elements of the blood, certain alterations were consistently reported. Vaughn, as early as 1892, noted that a leukocytosis followed the subcutaneous injection of nuclein. His observations were confirmed by Brown and Ross, who found there was always a leukocytosis 4 to 10 hours after an intramuscular injection of sodium nucleinate. In their series the counts went as high as 23,000 and returned to normal in from 3 to 5 days. Cowie and Calhoun report a series of 10 patients treated with intravenous injections of killed typhoid bacilli. They observed that such an injection almost invariably initiated a leukopenia which was followed by a leukocytosis, due chiefly to an increase in the granular leukocytes. In the latter paper, attention is also called to the fact that there is a stimulation of the mesenchymal fundaments which is expressed by the presence of myelocytes and nucleated red cells in the circulation.

**Methods and Materials.** In the 28 patients studied, the diagnoses may be roughly classified as follows: Focal infection with acute manifestations, 17; and focal infection with chronic manifestations, 11. There were 15 males and 13 females. Of the 28 patients, 16 received a second injection of killed organisms on an average of 4.7 days after the first injection. In this group there were 9 patients with focal infection with acute manifestations and 7 with focal infection with chronic manifestations. Divided as to sex, there were 10 males and 6 females.

In each case a control count was made immediately preceding the injection. In many instances a blood count 12 to 24 hours preceding the injection had been obtained, but such counts have been considered only as checks on the control counts. Following the injection of the killed typhoid and paratyphoid bacilli a complete blood count was made at hourly intervals for a period of 4 hours. Twenty-four hours after the injection another complete blood count was taken. With few exceptions the blood counts were made by the same person, and the differential count in all instances was checked by one of us. In the differential counts particular attention was paid to the immature forms, and on the original protocols the Schilling count and shift were recorded.

The bacterial vaccine used was Eli Lilly and Company's V-765, each cubic centimeter containing killed typhoid bacilli, 1000 million; paratyphoid bacilli A, 500 million; and paratyphoid bacilli B, 500 million.

The first dose of vaccine injected intravenously averaged 0.075 cc. per patient, an equivalent to 75 million killed typhoid bacilli, 37,500,000 killed paratyphoid A and 37,500,000 killed paratyphoid B bacilli. In the group of patients receiving a second injection of killed organisms, the average dose was 0.15 cc., which represented 150 million killed typhoid bacilli, killed paratyphoid A and B, each 75,000,000. The maximum dose was 0.2 cc. and the minimum 0.05 cc.



GRAPH I.—Average total leukocyte counts following the first and second injections of killed organisms.

**Observations.** Graph I shows the average total leukocyte counts following the first and second injections of killed organisms. The similarity of the two curves is most striking. In this graph there is not an actual leukopenia represented, as the control count of 20 patients showed a total leukocyte count of over 5000. A drop in the leukocyte count occurred in 21 of the 28 cases, with an average decrease of 4665; whereas 6 gave an average increase of 99.1. In one examination the count remained the same. Upon comparing the results obtained at the end of the first hour following the first and second injections, no consistent individual reaction was found, and the size of the dose administered did not seem to influence the count.

In the second hour there occurs following both injections a recovery from the relative leukopenia to almost the pre-injection count. In this hour's counts we find following both the first and

second injection 5 patients with a decrease in their leukocyte count. Of this number there was only 1 who showed a decrease in both the first and second hours.

The third hour counts gave a continued increase. There was approximately the same number of patients whose counts opposed the general trend as was observed in the preceding 2 hours. The maximum total leukocyte count following the first injection of killed organisms occurred in this hour's count.

In the fourth hour the count following the first injection remained the same, whereas following the second injection the maximum count was obtained. Again a small percentage of the counts showed a decrease.

One more series of counts was obtained 20 hours later, or 24 hours after the injection of the killed organisms. In both curves there was a decrease in the total leukocyte count, the counts following the first injection dropping to a lower level than those following the second. After both injections the final counts were higher than the control counts. At the end of 24 hours there was again a discrepancy in that a few patients showed an increased leukocyte count over the count immediately preceding.

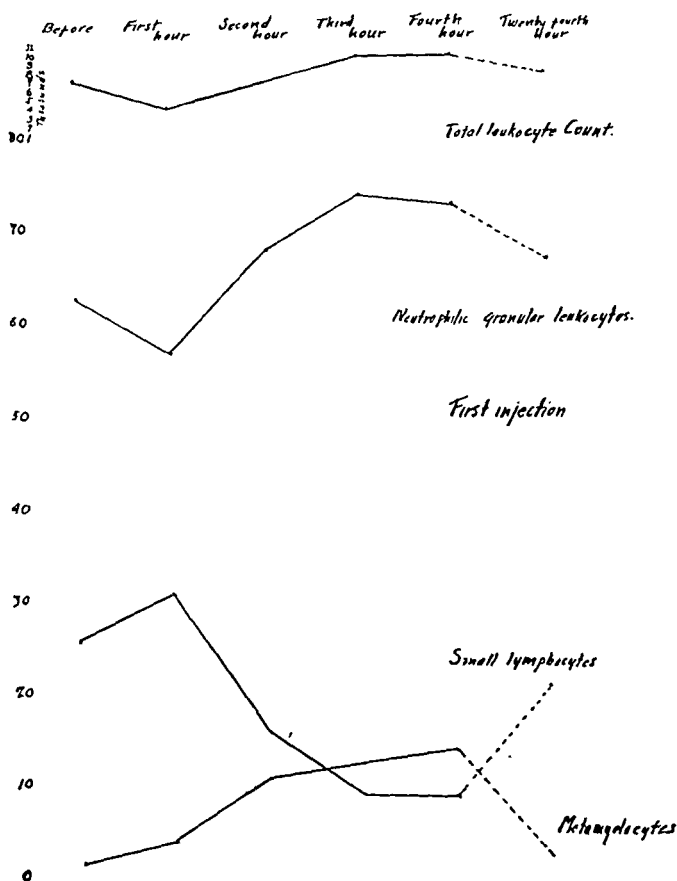
Following each injection of killed organisms the blood studies consisted of hemoglobin determinations, a count of the red blood cells, white blood cells, color index and a complete differential count. The only significant findings occurred in the leukocyte count and in variations in the number of neutrophilic granular leukocytes, small lymphocytes and metamyelocytes.

On Graph II are shown the total leukocyte count, the average neutrophilic granular leukocytes, the small lymphocyte and the metamyelocyte count, the latter 3 expressed in percentage. The counts from which these curves were plotted were obtained after the first injection of killed organisms.

It will be recalled that 28 patients were examined in this group and that the total leukocyte count was discussed in a preceding paragraph. The trend of the total leukocyte counts, the neutrophilic granular leukocyte and the metamyelocyte counts is most striking. The period of relative leukopenia corresponds with a decrease in the number of neutrophilic granulocytes, although during this period the metamyelocytes definitely increased. In almost every instance the metamyelocyte increase preceded the neutrophilic granulocyte increase by 1 hour. The maximum degree of increase of the metamyelocytes always occurred during the second hour, although the maximum percentage was not attained until the fourth hour. Comparing the neutrophilic granular leukocyte and metamyelocyte curves it is noted that they are almost parallel except during the first hour.

The curve representing the lymphocyte count is quite consistent. This type of cell increases in number during the period of leukopenia,

but rapidly falls to below normal level as well as the control level during the second, third and fourth hours. The upward trend occurs between the fourth and twenty-fourth hours, but the final count does not equal the control. In addition it will be noted that this curve is just the reverse of that of the neutrophils and total leukocyte count.



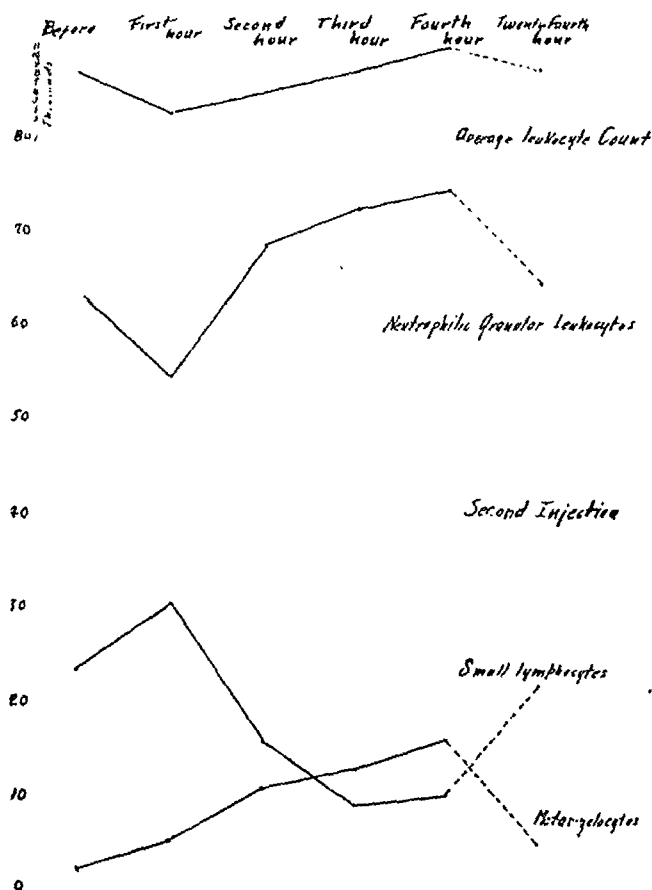
GRAPH II.—The total leukocyte count, the average neutrophilic granular leukocyte, the small lymphocyte and the metamyelocyte counts following the first injection of killed organisms.

In all the examinations there were counts whose trends were at variance with the majority, but in no instance did this variance persist in the same patient. This statement in turn holds true for the next group.

Of the 28 patients previously discussed, 16 had a second injection of vaccine. Graph III represents as before the average total leukocyte count and the average percentage of neutrophils, small lymphocytes and metamyelocytes. The trends of these curves are identical with those following the first injection, and it is noticeable

that the total count varies little even though the average dose is almost doubled.

Of most interest to us in the study of these differential cell counts were the cells of the myeloid series. As has been previously mentioned, the neutrophilic granular leukocytes closely followed the total leukocyte curve and at the peak of the curve many young adult granular leukocytes were found. The immature forms of the myeloid series that had made their appearance early in the reaction



GRAPH III.—The total leukocyte count, the average neutrophilic granular leukocyte, the small lymphocyte and the metamyelocyte count following the second injection of killed organisms.

reached their maximum number at the same time. These immature forms were, with the exception of 2 instances, all metamyelocytes of the neutrophilic type.

In the 220 blood counts studied, 5 myelocytes were found, and these occurred in 2 patients following the first injection. In 1 patient there was found 1 myelocyte in the third, and 3 in the fourth hour. The remaining cell was found in the 24-hour count of the second patient.

Our findings in this respect differ from those of Cowie and Calhoun who report that myelocytes were found quite regularly after injection in 24 out of 29 reactions. In their series they also observed that nucleated red cells were found in 7 out of 10 cases, while in our series they occurred in only 2 examinations. As the total number of nucleated red cells found was only 3, and as 2 of these were in the same count, we do not consider their presence significant.

**Discussion.** Many theories have been advanced to explain the results that occur following intravenous foreign protein medication, but no theory has been generally accepted. It is thought that the beneficial results obtained are due primarily to a strengthening of the immunogenic system of the body. Resistance or immunity is dependent upon the formation of substances known as antibodies. Phagocytosis of invading organisms by certain strains of leukocytes is another important factor in the recovery of a patient from bacterial disease, in fact, in discussing the subject of resistance, immunity and phagocytosis cannot be separated. Where antibodies are formed has been the subject of much experimental work, and the most generally accepted theory is that some antibodies are formed locally, while others appear to be formed simultaneously throughout the body. In the literature suggestions are found that the reticulo-endothelial system is the site of formation of these substances, but such an activity has not been satisfactorily demonstrated. Piney states that "The failure to obtain decisive results is doubtless due in part to the impossibility of completely ablating the function of the cell and so reducing the formation of these substances."

Inasmuch as neutrophilic granular leukocytes are phagocytes and, if one adheres to the view held by the monophyletists, that these cells originate from fixed cells that are known to have phagocytic powers, it may be inferred that there has occurred a stimulation of the reticuloendothelial system with the resulting formation of new phagocytic forms and a more rapid phagocytosis of the offending organisms. On the other hand, if the reticuloendothelial system is the site of the formation of antibodies the stimulation that it has received may have resulted in the production of more immune bodies. Judging from the type of immature cells that are found in the circulation following injections of foreign proteins, such a stimulation has occurred, and the beneficial results that the patients received may be due to either one of the two previously mentioned factors, although fever and vasomotor dilatation may also be important.

In this paper we do not attempt to prove that the beneficial results obtained are due either to the phagocytic action of the leukocytes or to an increase in the immunogenic substances in the body. We do not think, however, that the increase or decrease in the number of the leukocytes, especially the granular type, does indicate the degree of reaction of the reticuloendothelial system to the foreign protein injected.

**Conclusions.** 1. The significant hemocytologic changes following intravenous typhoid vaccine therapy are found in the leukocyte count, the neutrophilic granular leukocytes, metamyelocytes and lymphocytes.

2. Following the injection of the killed organisms a relative leukopenia occurs in the first hour followed by a return to pre-injection level in the second hour. In the third and fourth hours there is a leukocytosis, followed by a drop to almost pre-injection level at the twenty-fourth hour.

3. The neutrophilic granular leukocyte response closely parallels the response of the total leukocytes.

4. The metamyelocytes show no initial decrease but a steady increase during the first 4 hours; their number at the end of 24 hours is practically normal.

5. The lymphocytes show an increase in the first hour with a decrease in the following 3 hours. The 24-hour count shows an increase to near pre-injection level.

6. These hemocytologic changes are transient, as evidenced by the fact that the counts at the end of 24 hours had returned to the pre-injection level.

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### A STANDARDIZED TECHNIQUE FOR THE BLOOD SEDIMENTATION TEST.

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IN the description of a technique for the macroscopic examination of blood, it was elsewhere<sup>1</sup> stated that the hematocrit employed could be used not only for the determination of volume of packed

red cells, volume of packed white cells and platelets, and of icterus index, but also for the determination of sedimentation rate. The introduction of this hematocrit for the latter purpose, in spite of the fact that a great variety of sedimentation tubes is already available, is justified because this instrument may be employed with little additional effort for the other purposes mentioned and because the sedimentation rate may, by the determination of the volume of packed red cells in the same instrument, be very readily corrected for degree of anemia. It has been repeatedly demonstrated<sup>2,3,4,5</sup> that a reduction in the number or mass of red corpuscles of itself leads to a decreased suspension stability of the blood, and that allowance must be made for this factor in determining the true sedimentation rate of the red corpuscles.

Various investigators have shown<sup>2,5,6</sup> that a number of factors influence the sedimentation rate of erythrocytes. The following studies were made with the purpose of evaluating these factors as influencing sedimentation of red corpuscles in the hematocrit used by us<sup>1</sup> and with the object of defining the conditions under which this instrument should be employed.

**Probable Error of the Determinations.** With the object of determining with what precision sedimentation readings may be made on the same sample of blood, 9 experiments were carried out, in each of which 6 hematocrits were filled with blood and read at the end of 1 hour. The sedimentation rate of these bloods ranged from 2 mm. to 69 mm. The standard deviations of the readings in each experiment ranged from 0.13 to 0.89 mm. and averaged 0.48 mm. It may, therefore, be concluded that determinations in different tubes must be considered as not significantly different unless their difference is greater than 2 mm., which represents more than twice the greatest observed standard deviation.

**Effect of Anticoagulant.** Rourke and Plass<sup>6</sup> showed that heparin does not alter the sedimentation rate of red corpuscles. Consequently the influence of dry potassium oxalate, 2 mg. per 1 cc. of blood, which is the amount of anticoagulant recommended for use with the hematocrit,<sup>1</sup> was studied by comparing the sedimentation of blood collected in this way with that of blood collected in heparin (2 mg. per 5 cc. blood). A measured quantity of venous blood was mixed with potassium oxalate while another portion of the same blood was mixed with heparin. In 4 experiments the sedimentation rate of the samples was measured at 5-minute intervals for 1 hour, and at hourly intervals thereafter (Fig. 1); in 15 experiments readings were made at hourly intervals for 3 hours (Fig. 2).

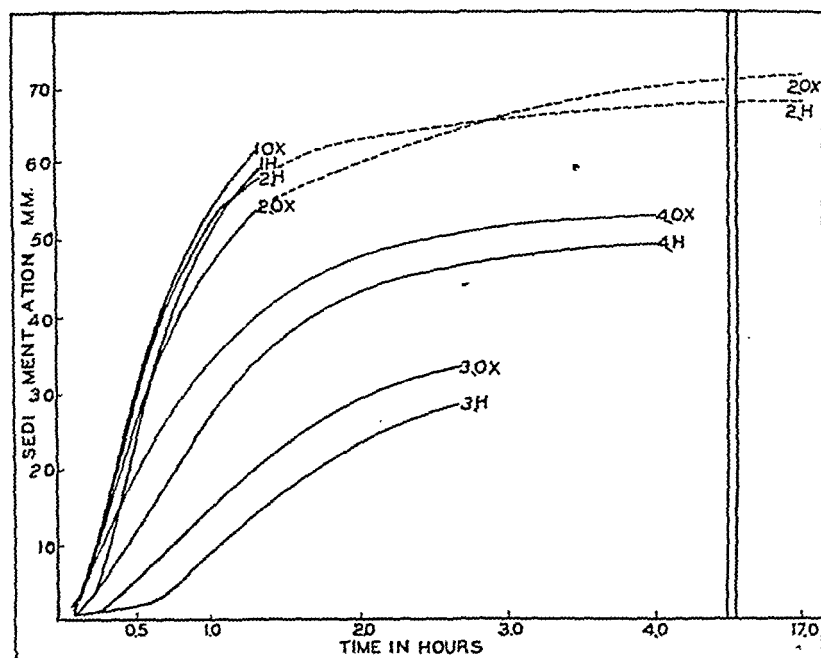
Contrary to the contention of Rourke and Plass,<sup>6</sup> we have found that potassium oxalate in the quantities employed is a satisfactory anticoagulant and does not depress the rate of settling. There was, on the whole, very good agreement, as Figures 1 and 2 indicate, between the sedimentation as recorded in oxalated blood and that in



heparinized blood. This was as true for readings made at the end of 2 and 3 hours as after 1 hour.

The disagreement between our observations and those of Rourke and Plass can probably be accounted for in part by the somewhat lower concentration of oxalate which we have used (10 as compared with 14 mg. per 5 cc.). We have, however, failed to note a consistently depressing effect on sedimentation even of greater quantities of potassium oxalate (Fig. 3) such as these investigators describe.

FIG. 1.—SEDIMENTATION RATE OF BLOOD COLLECTED IN SOLID POTASSIUM OXALATE (10 MG. PER 5 CC. OF BLOOD) COMPARED WITH THAT OF BLOOD COLLECTED IN HEPARIN (2 MG. PER 5 CC. BLOOD).



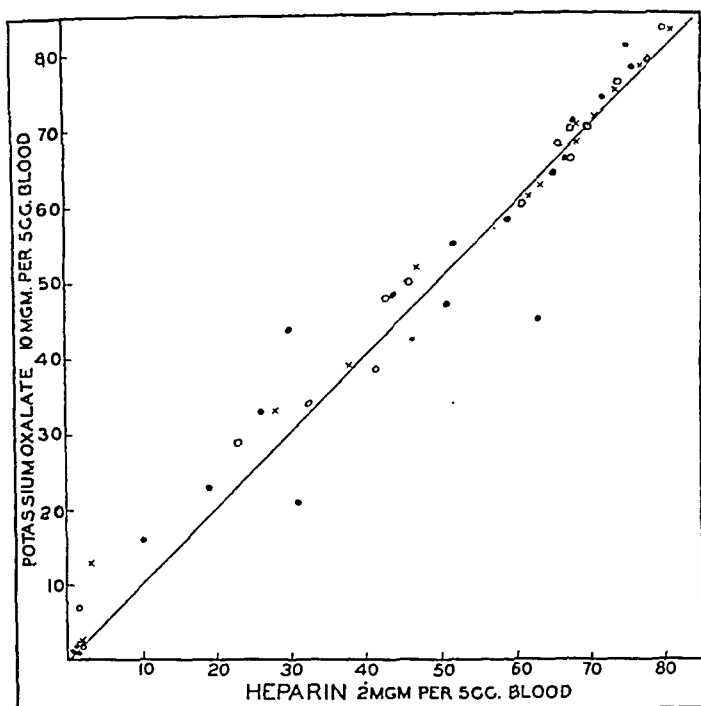
Curves to be compared are numbered 1.OX and 1.H, 2.OX and 2.H, etc. During the first hour of sedimentation, readings were made at 5-minute intervals.

Following the suggestion of Heller and Paul\* we have commenced to employ as an anticoagulant for human blood, a mixture of ammonium oxalate and potassium oxalate (6 mg. of the former and 4 mg. of the latter per 5 cc. blood). In these proportions no difference in the volume of packed red cells as compared with the volume in heparinized blood has been noted and, consequently, no correction for shrinkage is necessary. In a series of experiments the sedimentation rate of blood collected in this new anticoagulant mixture agreed, within limits of technical error, with that of heparinized blood both when readings were made at 5-minute intervals and when only at the end of 1 hour.

\* J. Lab. and Clin. Med., 19, 777, 1934.

**Influence of Bore and Length of Tube.** From a large sample of blood collected in potassium oxalate in the concentration of 10 mg. per 5 cc., a series of tubes of different lengths and bores was filled and sedimentation readings were made during the same period of time and under similar conditions. This experiment was repeated 7 times. The results, shown in Table 1, indicate that length of tube is a factor in influencing the sedimentation of erythrocytes. As was to be expected, the longer the tube, the greater was the distance traversed by the sedimenting red corpuscles. It must be observed,

FIG. 2.—CORRELATION OF SEDIMENTATION RATES OF BLOOD COLLECTED IN SOLID POTASSIUM OXALATE AND IN HEPARIN.

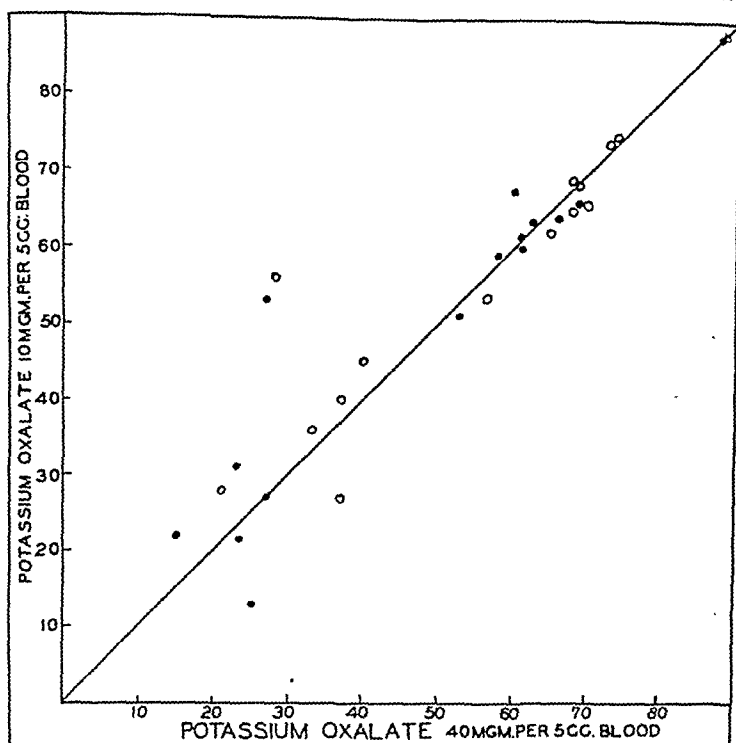


The solid circles represent readings at the end of 1 hour, the open circles readings at the end of 2 hours, and the crosses readings at the end of 3 hours. The averages of all the readings at the end of these periods of time for oxalate and for heparin, respectively, were 43.5 and 42.6 mm., 48.9 and 47.2 mm., 54.7 and 52.6 mm.

however, that distance traversed was not directly correlated with distance to be traversed, for in the tube 300 mm. in length (No. 4) the sedimentation was only slightly greater than in tubes one-third this length (Nos. 1 and 5). In fact, the readings at the end of the first hour in Nos. 1, 2, 4 and 5 were quite similar and in all but the longest tube (No. 4) this similarity was present, though to less extent, in the 2d and 3d hours. In contrast to the continuing sedimentation after the 1st hour in the longer tubes (Nos. 4, 1, 5 and 2) it is of interest to note that in the shortest tubes (Nos. 3

and 6), little further change took place after the 1st hour, the "stage of packing"<sup>7</sup> having apparently been reached.

FIG. 3.—CORRELATION OF SEDIMENTATION RATES OF BLOOD COLLECTED IN LOW AND IN RELATIVELY HIGH CONCENTRATIONS OF SOLID POTASSIUM OXALATE.



The solid circles represent readings at the end of 1 hour, the open circles at the end of 2 hours. The averages of all the readings at the end of these periods of time for 10 mg. and for 40 mg. oxalate, respectively, were 49.9 and 47.9 mm., 56.9 and 55.2 mm.

TABLE 1.—EFFECT OF BORE AND LENGTH OF TUBE.

Time in hours.	Sedimentation in millimeters.															
	Tube: 1*		2		3		4		5		6		7		8	
	L 100	B 2.5	L 70	B 2.5	L 35	B 2.5	L 300	B 6.0	L 100	B 6.0	L 35	B 6.0	L 40	B 4.5	L 40	B 11.0
1	31.0		26.0		17.0		35.0		28.5		17.0		21.0		20.0	
2	45.5		36.0		19.5		75.0		43.0		20.0		28.0		27.0	
3	58.5		45.0		21.0		104.5		50.5		22.0		30.0		29.5	

L and B represent length and internal diameter, respectively, in millimeters.

\* Author's hematocrit.

Within the ranges observed, namely, 2.5 to 11 mm., it does not seem that the bore of the sedimentation tube is of significance when columns of blood of equal height are compared. It has been pointed

out, however,<sup>5,8</sup> that tubes less than 2 mm. in internal diameter are unsatisfactory because sedimentation is uneven in such tubes.

**Inclination of the Tube.** It has been repeatedly demonstrated<sup>8,9,10</sup> that a deviation of the sedimentation tube from the perpendicular position causes an acceleration of the sedimentation rate. From our own observations (Table 2) in a tube 100 mm. in length, it appears that an inclination of as little as 2.3% causes an acceleration of 30%. The physical basis for the increased sedimentation rate in inclined tubes is clearly explained by Ponder.<sup>9</sup>

TABLE 2.—INFLUENCE OF INCLINATION OF TUBE.

Inclination of tube.	Vertical.	0.4°	1.0°	2.0°	2.3°	3.0°	4.0°	5.0°	6.5°	10.0°	15.8°	16.0°	23.5°
Sedimentation in 1 hour, mm.	30.0	29.0	....	....	39.0	....	....	....	....	44.0	....	43.0	....
Sedimentation in 1 hour, mm.	17.0	....	17.5	17.0	....	22.0	24.0	25.5	....	....	....	....	....
Sedimentation in 1 hour, mm.	10.5	....	....	....	....	....	....	....	14.0	....	30.0	....	31.5
Error due to inclination, per cent	..	3	3	0	30	29	41	50	33	47	186	43	200

**Effect of Temperature.** All observers<sup>6,11,12</sup> agree that the temperature of the room or receptacle in which the sedimentation test is carried out influences the sedimentation rate, there being increased settling with rising temperature. Our own experiments, carried out under controlled conditions and in carefully regulated water baths, show a consistent increase in rate as temperature rises. In Table 3, the means for 10 experiments on bloods with sedimentation rates ranging (at 22° C.) from 2 to 55 mm. are shown.

TABLE 3.—EFFECT OF VARIATIONS IN TEMPERATURE.

Temperature C.	10°	15°	20°	21°	22°	23°	24°	25°	26°	27°	28°	29°	30°	31°	32°
Sedimentation mm. in 1 hour	9.0	19.0	32.6	33.0	33.4	33.9	35.1	35.7	37.6	35.9	37.1	37.6	37.6	38.6	40.2

Westergren<sup>11</sup> has suggested that a correction of the sedimentation rate be made for the influence of temperature. Since the differences within the average range of temperature of most laboratories are small, it seems more practical to carry out the test in a room temperature of 22° to 27° C., modifications in technique being made only when temperature conditions are unusual. The effect of differences in temperature must be borne in mind particularly when the sedimentation readings are near the limit of normal or when the progress of a patient is being followed from time to time by means of this test.

**Changes in Suspension Stability of Blood as Influenced by Delay in Carrying Out the Test.** It has been stated<sup>6,11,13</sup> that a specimen of blood may be allowed to stand at room temperature for several hours without changing its suspension stability. We have found, however, that after 4 hours significant differences occur although in some instances these have not been noted sooner than 6 hours after the collection of the blood. Delay causes a decrease in the sedimentation rate. We have found no changes in sedimentation rate in samples of blood kept in a refrigerator (9° C.) and subsequently warmed to room temperature as long as the test has been carried out within 4 hours of the drawing of the blood.

**Miscellaneous Factors Which Appear to Exert No Significant Influence on Sedimentation Rate.** Under this head may be included: (i) the specific gravity of the red corpuscles themselves,<sup>14</sup> or their size;<sup>14</sup> (ii) aëration of the blood or loss of carbon dioxid;<sup>6</sup> (iii) the collection of blood from arteries or veins;<sup>15</sup> (iv) centrifuging the blood and subsequently remixing the cells and plasma;<sup>6</sup> (v) the ingestion of food,<sup>6</sup> and (vi) short violent exercise.<sup>6</sup>

**The Concentration of the Suspension.** It has been repeatedly demonstrated<sup>2,4,6,13,16,17,18</sup> that the concentration of the blood is a very important factor in influencing the sedimentation rate, the more dilute the blood the greater being the speed of settling. Fähræus<sup>19</sup> has pointed out that this relation is not direct or linear, there being, *cæteris paribus*, less tendency to aggregate in blood sparse in red corpuscles. The influence of concentration has been shown to be so great, that a number of investigators have recommended that the observed sedimentation rate be corrected for the degree of dilution (anemia) or concentration (polycythemia) of the blood. This may be done by taking into account the red cell count,<sup>5</sup> the hemoglobin content<sup>20</sup> or the volume of packed red cells.<sup>3,21</sup>

By far the simplest procedure is to make a correction according to the volume of packed red cells for, if the hematocrit is used for determining sedimentation rate, all that is required is centrifugation of the tube after the sedimentation rate has been determined.

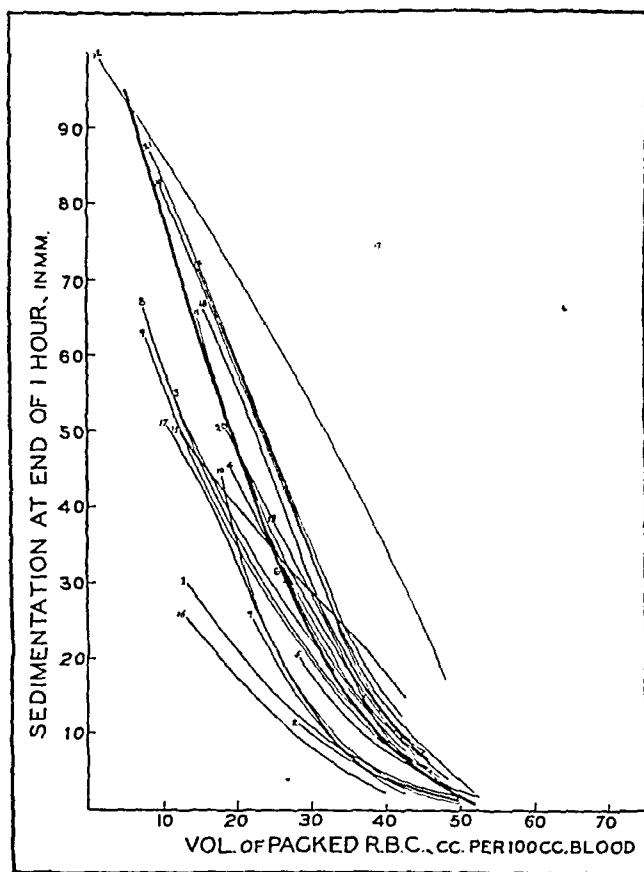
Rourke and Ernstene<sup>3</sup> have prepared a chart for correcting the sedimentation rate as judged by the "period of constant sedimentation" or period of most rapid fall and have devised a "corrected sedimentation index." Their chart may be satisfactorily employed in connection with the hematocrit employed by us for this instrument is of the same length and only of slightly less inside diameter than the tube of Rourke and Ernstene.

The determination of the "corrected sedimentation index" of Rourke and Ernstene requires the recording of degree of settling at frequent intervals. This may be satisfactorily done by photographic means,<sup>22</sup> but the requisite apparatus is not available to every laboratory, and to read the degree of sedimentation every few minutes requires time and seriously detracts from the simplicity

which is the outstanding merit of the sedimentation test. Consequently it was thought advisable to prepare a chart which would serve to correct the sedimentation rate as read at the end of 1 hour.

Data for the preparation of a correction chart were obtained as follows: A large sample of blood was collected in solid potassium oxalate, 10 mg. per 5 cc. of blood. The sedimentation rate of this

FIG. 4.—CORRELATION OF SEDIMENTATION RATE AND VOLUME OF PACKED RED CELLS.



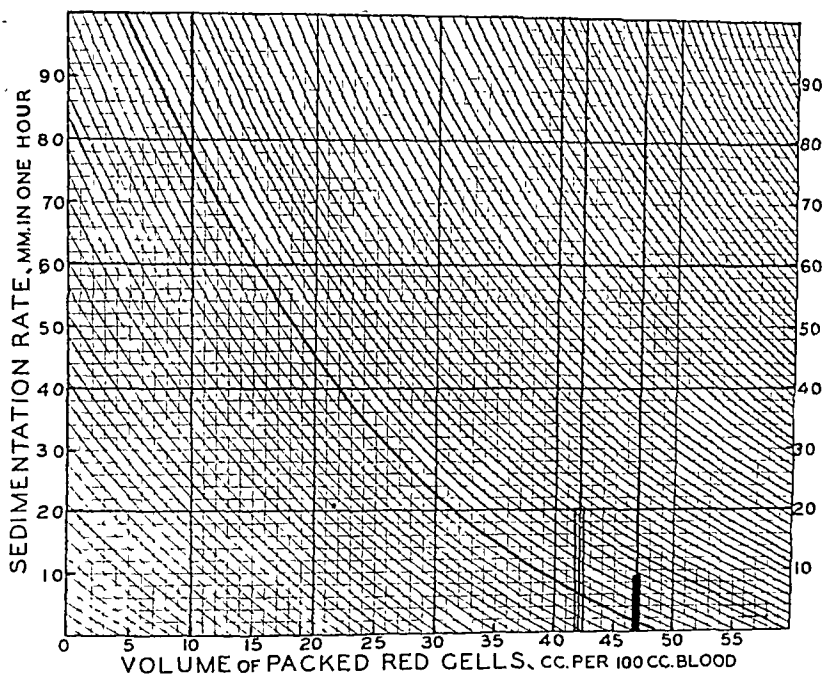
Each curve represents an experiment in which successive dilutions of blood were made with plasma and sedimentation rate was determined for each sample so prepared. Curves 1 to 13 are derived from the blood of normal men, Curves 14 to 21 are from the blood of normal women. The curve outlined most heavily is a logarithmic curve based on these observations.

blood and the volume of packed red cells were determined. Subsequently, the blood was diluted with increasing quantities of its own plasma and the rate of settling and volume of packed red cells were determined on each sample of diluted blood. In this way 6 to 9 dilutions were made with each sample. The determinations were made under the conditions already outlined as necessary for the accurate performance of the sedimentation test. Twenty-one

experiments were carried out in this way. The blood was obtained from 13 normal men and 8 normal women. The sedimentation rates in these experiments varied from 1 to 98.5 mm. in 1 hour and the volume of packed red cells ranged from 52.5 to 1.5 cc. per 100 cc. of blood. The curves for each of these bloods are shown in Figure 4.

Analysis of these data revealed a high degree of correlation between sedimentation velocity and volume of packed red cells, the lower the latter, the greater being the rate of settling. The correlation coefficient was  $-.8642 \pm .0127$ . Comparison with the correlation ratio which was .9202 showed, however, that the correlation was non-linear,  $\zeta$  being  $.1000 \pm .0304$ .

FIG. 5.—CHART FOR CORRECTING SEDIMENTATION RATE FOR VARIATIONS RESULTING FROM DIFFERENCES IN THE CONCENTRATION OF RED CORPUSCLES AS MEASURED BY VOLUME OF PACKED RED CELLS.



The logarithmic curve on which the chart is based is heavily outlined. The mean normal volume of packed red cells for men (47 cc.) and for women (42 cc.) are also heavily outlined and the range of normal sedimentation is represented by solid and open columns for each sex, respectively.

Since the correlation for the data obtained for male blood ( $-.8970 \pm .0132$ ) was not very different from that obtained for female blood ( $-.8680 \pm .0196$ ) and since the individual curves for the two sexes did not seem to differ, all the data obtained were utilized for the preparation of a corrective curve. A logarithmic curve of the formula,  $y = 44.97 - 1.37x - 23.4 \log x$ , was found to best fit the observations.

A correction chart which has been prepared on the basis of this curve is shown in Figure 5. An example will serve to explain how the chart may be used.

Let it be supposed that the sedimentation rate of the blood of a female patient is 40 mm. in 1 hour and that the volume of packed red cells is 25 cc. per 100 cc. of blood. The horizontal line at 40 on the chart is followed to the right as far as the point at which the vertical line rising from 25 meets it. The curved line nearest this point is then followed downward and to the right, as far as the normal line for volume of packed red cells in women. It is found that the curve in this instance meets the normal line opposite 11 mm. Consequently the "corrected" sedimentation rate is 11 mm. This is well within the range of sedimentation in the blood of normal women. It is assumed that the original sedimentation rate of 40 mm. is no greater than would be expected if the blood of a normal woman had been diluted to 25 cc. of packed red cells per 100 cc. blood. However, if the sedimentation rate for this blood had been found to be 70 mm. while the volume of packed red cells remained the same (25 cc.), the corrected sedimentation rate would be 30 mm. Since this is distinctly greater than normal, the inference is drawn that the sedimentation rate of this blood is greater than can be accounted for by the anemia alone.

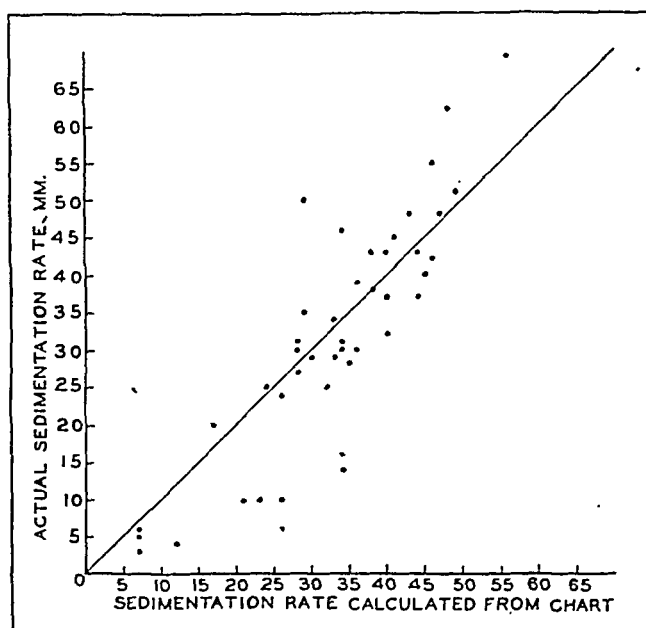


FIG. 6.—CORRELATION OF ACTUAL AND CALCULATED SEDIMENTATION RATES.  
CORRELATION COEFFICIENT,  $.7950 \pm .0272$ .)

The accuracy of this chart was tested in the following manner. Blood was obtained from a series of 31 patients suffering from a variety of ailments and having various grades of anemia. Sedimentation rate and volume of packed red cells were determined. The blood was then concentrated by withdrawing plasma, and sedimentation rate and volume of packed red cells were again determined.



Frequently this procedure was repeated and thus a total of 45 determinations were carried out. In Figure 6 the relation of the sedimentation rate actually found after concentration of the blood, is compared with the sedimentation rate calculated for the original sedimentation rate and volume of packed red cells at the level of packed red cells found in the concentrated blood. It will be seen that the correlation, although not perfect, is nevertheless quite high.

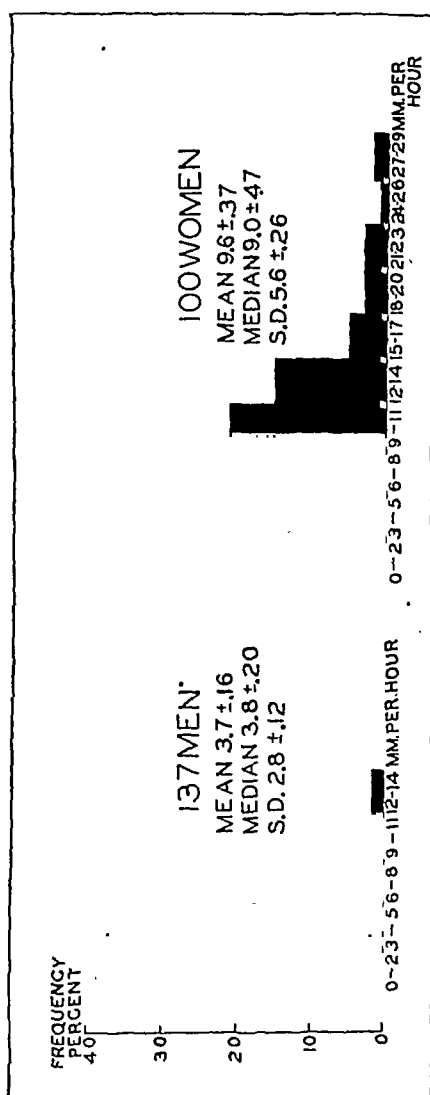


FIG. 7.—FREQUENCY DISTRIBUTION OF SEDIMENTATION RATE IN 137 MEN AND 100 WOMEN.

**Sedimentation Rate in Normal Adults.** Blood was obtained from 137 men and 100 women. The men were medical students who had received a complete physical examination 1 to 4 months prior to the blood examination. As far as can be judged by history, physical examination, roentgenograms of the chest, blood counts and Was-

sermann tests, these men were in excellent health and none suffered from even a mild infection at the time of blood examination. The women included a number of medical students but were chiefly nurses. With the exception of roentgenograms of the chest, the latter were judged to be in good health by the same tests as the medical students. The sedimentation test was carried in the manner already outlined<sup>1</sup> and the precautions already considered were observed. Red cell counts, hemoglobin and volume of packed red cells were determined on the same samples of blood and these have been reported elsewhere.<sup>23</sup>

The frequency distribution as well as other statistical data for these observations are presented in Figure 7. It will be noted that the mean for men is much lower than that for women and also that the variation in sedimentation rate in the latter is much greater than among the men. The variation observed in the men was only slightly correlated with volume of packed red cells, the correlation coefficient being  $-.2334 \pm .0545$ . Among the women no correlation was observed between sedimentation rate and volume of packed red cells, the correlation coefficient being  $-.0258 \pm .0650$ .

The data available do not afford any evidence concerning the cause of the wide variation in sedimentation rate in the women. The date of the last menstrual period was recorded when the blood was drawn for the sedimentation test but the information gathered fails to reveal significant information. The mean sedimentation rate during the first postmenstrual week was 10.2 mm.; during the 2d week, 9.3 mm.; during the 3d, 8.6 mm., and during the 4th week 10.9 mm. Although these figures show somewhat higher values in the weeks immediately preceding and following menstruation, the differences are too small to permit conclusions to be drawn. Greisheimer<sup>24</sup> noted a greater variation in sedimentation rate in women as compared with men but did not find that this was related to the menstrual periods as earlier observers had suggested.

In setting the maximum limits of normal variation in sedimentation rate, it is probably quite adequate to consider the mean value plus or minus twice the standard deviation, since this includes 95.45% of all the variates. This would set the limit of normal in men at 0 to 9 mm., and in women 0 to 20 mm. In the great majority of normal men sedimentation rate should really be no greater than 6.5 mm., and in women no greater than 15 mm. These values represent 86.4% of all the variates observed.

**Summary and Conclusions.** The influence of various factors on the suspension stability of the blood has been studied, conditions for its accurate performance have been considered, and the normal sedimentation rate under these conditions determined.

The use of a special hematocrit is recommended for the determination of the sedimentation rate because the same instrument can be used subsequently for the measurement of volume of packed red

cells, volume of packed white cells and platelets, and icterus index. The determination of volume of packed red cells is especially valuable because by this means the sedimentation rate may be corrected for alterations due to anemia.

The following appears to be a satisfactory and accurate method of procedure:

**Method.** 1. Five cc. of venous blood is collected by means of a dry syringe and needle and mixed in a small bottle containing 4 mg. solid potassium oxalate and 6 mg. solid ammonium oxalate. This concentration of oxalate does not alter the sedimentation rate as compared with that of blood collected in heparin. Less than 1 cc. of blood is needed for the sedimentation test. The remainder can be used for other blood examinations.

2. The blood so collected should be used for the determination of sedimentation rate within 4 hours of its time of collection. Further delay may be associated with increased suspension stability of the blood.

3. The hematocrit is filled to the 10 cm. mark with blood. The upper level of sedimenting corpuscles may be read at frequent intervals or, more simply, a single reading may be made at the end of 1 hour.

4. Since sedimentation rate increases with increasing temperature, the sedimentation test should be carried out at a temperature not less than 22° nor greater than 27° C. Within this range variations resulting from differences in temperature are small. If the blood used has previously been kept in a refrigerator it should first be permitted to attain the above temperature before being used.

5. The hematocrit should be kept in an exact vertical position during the sedimentation of the blood corpuscles, for when the instrument stands at an angle of even 3° from the vertical, significant acceleration of sedimentation takes place.

6. After sedimentation rate has been determined, the hematocrit containing the blood should be centrifugalized and volume of packed red cells determined. The sedimentation rate may then be corrected for alterations due to anemia. A correction chart is presented.

The average sedimentation at the end of 1 hour has been found to be, in healthy men, 3.7 mm. and, in normal women, 9.6 mm. In 86% of the men examined the sedimentation rate ranged from 0 to 6.5 mm., whereas in the same proportion of women the sedimentation rate ranged from 0 to 15 mm. In an additional 9% the sedimentation rate ranged as high as 9 mm. in men and 20 mm. in women. These values probably represent the extreme range of normal variation under the conditions outlined.

We are indebted to Mr. Wilbur Rigger for technical assistance.

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## MACROCYTIC ANEMIA AND HEPATIC CIRRHOSIS.

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THE not infrequent occurrence of a blood picture in hepatic cirrhosis that approaches that of pernicious anemia during remission has been widely recognized but not sufficiently appreciated. The purpose of this communication is to report the blood pictures of 12 cases of portal cirrhosis and to present the data obtained from a review of 41 case records.

The fact that the patients showing this type of blood picture do not resemble clinically pernicious anemia, plus the fact that such descriptive terms as "pernicious anemia-like blood picture" or "a blood picture that closely resembles pernicious anemia" are cumbersome, lengthy and inflexible, seems to justify the coining of an appellation such as pernicioid (pernicious-like) anemia. Therefore, this term will be used in the following discussion.

**Review of Literature.** Recent reports calling attention to this pernicioid, or pernicious anemia-like, blood picture have been made by Wintrobe and Shoemaker, Goldhamer, Van Duyn and others. An adequate review of a number of reports of less recent date has been presented in the article by Wintrobe and Shoemaker.<sup>1</sup>

Goldhamer<sup>2</sup> reports such a case of hepatic cirrhosis with free hydrochloric acid present in the gastric contents. Liver therapy produced a hemopoietic response similar to that observed in patients with true pernicious anemia. He suggests that an additional factor in the production of a blood picture resembling pernicious anemia may be interference with the storage of the material necessary for the maturation of red blood cells.

Van Duyn<sup>2</sup> reports 4 cases: 1 of hepatic cirrhosis, 2 with hepatitis and cirrhosis and 1 with chronic diffuse and acute hepatitis. Free hydrochloric acid was present in the gastric contents of all 4 patients. In a review of 28 case records of hepatic cirrhosis he found 5 (18%) with a high color index in the presence of an anemia. He points out a group of conditions which are associated with a macrocytic type of anemia and in which diseases of the liver are outstanding features and suggests that diseases of the liver should be given a place in the mechanism of the production of a macrocytic anemia.

Wintrobe and Shoemaker<sup>1</sup> report 11 instances of macrocytosis in 43 cases with various hepatic disorders. There is an absence of free hydrochloric acid in 6 of the 10 patients in whom gastric analyses were performed. The presence of the extrinsic factor of Castle was demonstrated in the gastric contents of 1 of these patients. A clear-cut response to liver therapy was not observed in 3 cases, but in the 4th a maximal response of reticulocytes occurred. They suggest that this macrocytosis may be the result of the inability of the damaged liver to store the hematopoietic substance formed by the interaction of Castle's intrinsic and extrinsic factors and by a combination of partial gastric disturbance and incomplete liver damage.

**Methods.** The methods used have been described by Musser and Wintrobe.<sup>4</sup> The average of 2 hematocrit readings was used in each determination. All erythrocyte counts reported are the average of 2 counts that check within 100,000. All hemoglobin determinations were made by the Newcomer method.

*Summary of 12 Cases Studied.* (Table 1.) A clinical diagnosis of portal cirrhosis was made in all cases without equivocation. Additional diagnoses, when present, are given in Table 1.

The average age was 54 years (extremes, 41 and 76). Their history of alcoholic consumption varied; 6 had long revelled in the false felicities of chronic inebriety; 2 professed abstemious lives, while the remaining 4 had used strong drink in moderate or negligible quantities. Free hydrochloric acid was absent in 6 of the 8 cases in which gastric analysis was performed. The first 4 cases are of special interest because they maintained a color index above 1, in spite of the fact that the portal cirrhosis was accompanied by conditions that are commonly associated with a microcytic hyperchromic type of anemia. Clinical jaundice was absent in all cases.

The color index was more than 1 in 9 cases; the average for the entire group was 1.09, the lowest 0.81, and the highest 1.36. The mean corpuscular volume was above 90 in 7, the average was 90.1, the lowest 80.7 and the highest 96.4. The increase in color index was more constant than the increase in cell size which was at the upper limit of normal. The average erythrocyte count was 4,039,000. Two of the cases had counts above 5,000,000. The total leukocyte count was below 5000 in 5 cases, above 7500 in only 2; the average for the 12 cases was 5840. The low white cell count emphasizes

the point brought out by King,<sup>6</sup> that the presence of leukopenia cannot be used as a criterion for the differential diagnosis of Banti's disease with secondary cirrhosis from portal cirrhosis.

TABLE 1.—ANALYSIS OF DATA OF 12 CASES WITH MACROCYTOSIS.

Case No.	M.C.V.*	Color index.	Hemoglobin, %.	R.B.C., millions per c.mm.	W.B.C., thousands per c.mm.	Free HCl.	Ascites.	Liver.	C <sub>2</sub> H <sub>5</sub> OH.	Additional diagnoses.
1 . . .	95.0	1.20	89.7	3.67	3.5	0	+	+	+	Alcoholic neuritis. Amebiasis. Uncinariasis. Tertian malaria.
2 . . .	83.4	1.36	103.0	3.76	5.5	0	+	+	+	
3 . . .	92.0	1.03	82.8	4.06	11.5	6	+	—	+	
4 . . .	91.0	1.26	48.3	1.98	3.7	0	?	+	+	
5 . . .	92.6	1.06	82.8	4.26	7.5	?	+	+	0	
6 . . .	94.0	1.01	79.0	3.94	..	0	+	+	0	Lues. Arteriosclerotic heart disease.
7 . . .	89.0	0.87	89.7	5.01	4.5	0	—	+	?	
8 . . .	80.7	0.96	96.0	5.10	6.2	—	+	+	?	
9 . . .	95.0	1.30	97.0	3.72	5.5	22	—	+	?	
10 . . .	96.4	1.16	58.6	2.59	4.0	—	+	—	?	
11 . . .	89.0	1.16	110.0	4.76	4.2	0	+	+	+	
12 . . .	84.3	0.81	75.9	4.60	7.6	..	+	—	+	
Aver. . .	90.1	1.09	..	4.04	5.8					

\* M.C.V. refers to mean corpuscular volume expressed in cubic microns.

*Report of 41 Case Records.* The records of 41 cases of portal cirrhosis admitted to the wards of Charity Hospital during the last 10 years have been reviewed in an effort to throw additional information on the incidence of macrocytosis and portal cirrhosis. The only criterion available was the color index. All hemoglobin determinations were done by the Tallqvist method, which is notoriously inaccurate.

Average age for this group was 53.5 years (extremes, 28 and 78).

*Physical Findings.* *Ascites:* ascites was present in 32 cases (62.7%). *Diarrhea:* diarrhea was present in 11 (21.5%). *Jaundice:* jaundice was present in 10 (19.6%). *Hemorrhage:* gastric hemorrhage was present in 7 (13.7%). *Tongue:* the tongue was recorded as atrophic or red in 7 (13.7%). *Blood pressure:* blood pressure was unusually low for the group, with an average age of 53.5 years. The mean systolic pressure was 121.9, and the mean diastolic, 75.4. Only 4 patients showed a diastolic pressure of 100 or more and all of these showed evidence of chronic nephritis.

*Laboratory Data.* *Gastric analysis:* gastric analysis was recorded in 18 instances; 11 patients (61.6%) showed a low figure for free hydrochloric acid; 3 of these were less than 10, the other 8 (44.4%)

showing an absence of free hydrochloric acid. *Blood picture:* the average white cell count was 7891; the average red cell count was 3,924,000. The total erythrocyte count was between 4,500,000 and 3,500,000 in 31 cases; 9 were above 4,500,000, and the remaining 3 were below 3,000,000. *Color index:* the average color index was 0.916; 14 (27.4%) showed a color index of 1 or more.

**Discussion.** It is of interest to see how much diagnostic value may be attached to the presence of this pernicious anemia. Its presence has been reported in so many different conditions in which the liver is adversely affected that it cannot be expected to point out any specific lesion of that organ, but it should suggest hepatic disease. It is conceivable, however, that a slight macrocytosis and a color index of more than 1 in the presence of hematemesis may serve as a criterion to differentiate hematemesis secondary to cirrhosis of the liver, from bleeding ulcer or carcinoma.\*

The first problem in estimating its diagnostic significance is to determine the frequency with which it occurs, and this cannot be done until a larger series of cases has been reported. In this limited group of 12, all but 1 (90%), with a red count below 5,000,000, showed a color index of more than unity. Judging from other reports and from the case records reviewed, it is probably only a coincidence that such a high percentage of this group should show this interesting finding.

Case 12 illustrates the pertinent fact that this blood pattern does not occur at any definite period in the progressive downward course of portal cirrhosis and that it does not depend on the degree of obstruction to the portal circulation. This patient's symptoms were of longer duration and the consequences of portal obstruction more marked than in any one of the other cases. Paracentesis had been repeated 17 times, but he did not develop a macrocytosis or high color index. His mean corpuscular volume was 84, color index 0.81 and the total erythrocyte count was 4,605,000.

When attempting to explain the etiology of this most interesting blood picture, one must remember that prodigal hypothesizing is cheap but not infrequently fallacious. The most logical hypothesis would seem to be that the portal obstruction and the concomitant gastric congestion adversely affect the formation of the nebulous intrinsic factor of Castle, but Wintrobe and Beebe have demonstrated the presence of this intrinsic factor in the gastric contents of one of their cases and, furthermore, a similar blood picture has been reported in other conditions in which there is no reason to believe that gastric function has been disturbed. Macrocytosis and a high color index have been reported in such seemingly intangible conditions as chronic hepatomegaly,<sup>1</sup> metastatic carcinoma of the liver,<sup>1</sup> acute catarrhal jaundice,<sup>1,7</sup> chronic passive congestion

\* Hemorrhage has also been shown to increase temporarily the diameter of the erythrocyte. (See Am. J. Physiol., 103, 407, 1933, and Quart. J. Exp. Physiol., 19, 145, 1928).

of the liver,<sup>1</sup> erythroblastosis fetalis,<sup>5</sup> congenital syphilis,<sup>5</sup> arseniuretted hydrogen gas poisoning,<sup>8</sup> infections of the gall bladder,<sup>9</sup> Weil's disease<sup>7</sup> and thrombosis of the portal vein,<sup>7</sup> but all of these seemingly unrelated conditions have one thing in common—that all is not well within Glisson's capsule. Therefore, the most plausible hypothesis is that disturbed hepatic function prevents the further elaboration or proper utilization of the anti-anemic substances formed by the interaction of the intrinsic and extrinsic factors.

**Summary and Conclusions.** 1. The blood picture in 12 cases of portal cirrhosis is reported, pointing out the tendency to macrocytosis and a high color index. Pernicioid (pernicious-like) anemia has been suggested as an appropriate term to apply to this condition.

2. A review of 41 case records of portal cirrhosis showed a color index of 1 or more in 27.4%.

3. The diagnostic possibilities of this type of blood picture have been briefly discussed.

4. Its production is attributed to hepatic abnormalities which prevent the further elaboration and utilization of the anti-anemic substances.

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## INTRAPLEURAL PRESSURE IN ARTIFICIAL PNEUMOTHORAX DURING PREGNANCY AND CHILDBIRTH.\*

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VALSALVA (1740) observed the effect of inspiration and expiration upon the circulation and thus described what has become known as "the Valsalva experiment." "If the glottis is closed after a

\* Read before The American Clinical and Climatological Association, Toronto, Canada, May 23, 1934.



deep inspiration and a strenuous and prolonged expiratory effort is then made, such pressure can be exerted on the heart and intrathoracic vessels that the movements and flow of the blood are temporarily arrested."<sup>1</sup>

This observation has been studied in more recent years, and through the use of modern technical procedures it has been shown by Mosler and Balsamoff:<sup>2</sup>

1. That there is a sharp increase in pressure in the bronchi and alveoli (Krause<sup>3</sup>) "because of which increased alveolar pressure the blood in the soft-walled capillaries is driven into the left heart and thence into the general circulation. A renewed influx of venous blood into the right heart cannot follow because the entrance to the right heart is narrowed by the venous trunks being compressed by the increased intrathoracic pressure. This severe pressure is transmitted not only to the lungs and bloodvessels, but also to the heart wall. As a result the complete emptying of the heart contents can occur—the heart pumping itself empty."

2. "That the diminished size of the heart during the Valsalva experiment is a real and not an apparent one due to rotation."<sup>2</sup> This observation has been more recently described by Moore and Wilson<sup>4</sup> under the name of 'cardiac squeeze.' In obstructive emphysema due to tracheal foreign bodies they found the heart measurements definitely smaller during the expiration."

Beck and Isaac<sup>5</sup> have shown in their studies on animals that the normal heart satisfactorily withstands exposure to atmospheric pressure, but the effect of "pneumocardiac tamponade" may persist for hours after the tamponade has been corrected and, if the heart cannot make the added effort to overcome this burden, it may after a long struggle completely fail.

With an increased intrapleural pressure the venous pressure is elevated and the circulatory rate is slowed,<sup>6</sup> and by increasing the intrapleural pressure in a pneumothorax the lymph flow may be reduced by as much as 50%.

The inhalation of carbon dioxid is accompanied by an increased negative intrapleural pressure, while on the other hand, in anoxemia there occurs a steadily rising pressure in the pleura, accompanied by an increase in the mean thoracic girth, as witnessed during an asthmatic attack.<sup>8</sup>

During the performance of an expulsory effort made with the glottis open, but blowing against resistance, it is possible to build up an intratracheal pressure of 250 mm. of mercury.<sup>9</sup> With the same expulsory effort made with the glottis closed, it would seem reasonable to suppose the pressure would be higher.

The involuntary occurrence of the Valsalva experiment takes place during the performance of heavy lifting or other laborious work, extreme athletic efforts, defecation and in childbirth. The

same effect occurs during severe whooping cough and stenosis of the larynx.<sup>10</sup>

The only reference we have found regarding the intrapleural pressure during the performance of the Valsalva experiment is by Kountz and associates,<sup>5</sup> but they permitted only a moderate expulsive effort—the intrapleural reading reached a positive of 12 cm. of water.

We have had several patients during an artificial pneumothorax refill make expulsive efforts with pressures ranging from +50 to +65 for women and +109 to +249 for men. A much lower value was reached during a laugh or cough—these and subsequent readings are recorded in centimeters of water.

We have not had the temerity to produce a very small pneumothorax to enable us to study the normal intrapleural changes during labor. However, we have had the opportunity of making observations upon artificial pneumothorax during delivery.

**Protocols.** CASE 1.—Multipara, aged 35. Right lung, 40% collapsed; duration, 1 month. Pulmonary tuberculosis. Delivered, August 28, 1932, at the Rochester General Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	-14	+ 5.0	Before onset of labor.
Gas oxygen:			
Deep . . . . .	-16	+ 7.0	Late 2d stage.
Light . . . . .	-12	+ 4.0	
Deep . . . . .	-16	+ 7.0	Head presenting.
Deep . . . . .	..	+83.2	Head presenting during pain.
Deep . . . . .	..	+85.8	Birth of head.
Deep . . . . .	+52	+57.0	Expulsion of placenta.
None . . . . .	+ 4	+11.0	
	- 9	+ 2.0	After 250 cc. refill given.

CASE 2.—Primipara, aged 22. Right phrenectomy, November 11, 1927. Artificial pneumothorax, 75% collapse; duration, 5 years. Bronchiectasis of right middle lobe. Delivered, August 18, 1933, at the Rochester General Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	-5	- 2	Beginning of refill.
	+8	+13	After 125 to 200 cc. air.
	-1	+ 4	End refill during 2d month pregnancy; mediastinum displaced.
	-3	+ 2	End refill 4th month pregnancy; mediastinum displaced.
Gas oxygen:			
Deep . . . . .	-5	+ 4	Head presenting.
Deep . . . . .	-6	+31	Head delivered.

Needle slipped out—no further readings.  
Voluntary experiment +50, +65.

Pressure since delivery has been further reduced to +1½ on account of movable mediastinum.

At the time of delivery the needle was inserted during a pain at

the same location used for a refill 2 weeks previously, but the diaphragm had risen further and the needle had to be reinserted an interspace higher to enter the pleura. Since delivery the same location is used as before for refills, the diaphragm having returned to its previous level.

CASE 3.—Primipara, aged 28. Left lung, 85% collapse; duration, 5 years. Pulmonary tuberculosis. Delivered, September 19, 1933, at the Genesee Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	-20	- 8	Refill, average before onset of labor.
	- 5	- 2	End 600 to 800 cc. air.
None . . . . .	-10	0	Between pains.
None . . . . .	-13	- 3	Between pains.
None . . . . .	+10	+26	During pain.
	+20	+35	During pain.
Gas oxygen:			
Deep . . . . .	+27	+45	During episiotomy.
Deep . . . . .	+24	+40	Head delivered.
None . . . . .	- 8	+ 1	After delivery.
None . . . . .	-11	+ 7	500 cc. refill.

CASE 4.—Multipara, aged 22. Left lung, 60% collapse; duration, 2 years. Pulmonary tuberculosis. Delivered by Cesarean section, October 31, 1933, at Strong Memorial Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	- 2	+2	End last refill 400 cc.
	- 3	-1½	Before operation begun.
Local . . . . .	-11	0	During injection of skin.
	-14	-8	
Gas oxygen:			
Light . . . . .	- 7	+5	
Deeper . . . . .	- 9	+3	Cutting skin.
Deep . . . . .	- 6	+4	Cutting peritoneum.
Deep . . . . .	- 4	+6	Cutting uterus.
Deep . . . . .	- 6	+4	Stitching uterus.
Light . . . . .	- 4	+1	Stitching skin.
Discontinued . . . . .	- 3	+2	End 75 cc. refill.

**Comment.** It would seem that as each of these patients was under deep gas-oxygen anesthesia and rebreathing approximately 2 to 5% CO<sub>2</sub> during the actual delivery, the intrapleural pressure readings are probably lower than would obtain in delivery without anesthesia.

The change in the rigidity of the mediastinum in Case 2, beginning at the 2d month of pregnancy, is puzzling. Prior to this time a rather high pressure was used to maintain collapse of the bronchiectatic middle lobe. If lower pressure was used, cough and expectoration returned, but with a well-maintained collapse none occurred, in spite of the fact that opaque oil injected into the collapsed lobe showed the bronchiectatic area still open and of almost the same size as before the treatment was begun. Since delivery the mediastinum remains less rigid and the intrapleural pressure has been still further lowered at refills.

Case 1 had by far the smallest pneumothorax and showed the highest pressure reading during labor. Case 3 had the largest pneumothorax, but showed higher readings than Case 2. However, in Case 2 the readings may have been affected by the fact that the mediastinum showed queer behavior and the diaphragm was fixed by a previous phrenectomy. In addition, Case 2 was the most frail of all the 3 normal deliveries.

While 4 cases constitute a very small number from which to draw deductions, nevertheless these observations suggest to us certain conclusions:

1. Is not delivery by Cesarean section preferable to spontaneous delivery in the presence of serious cardiac or pulmonary disease?

2. Is not the increased intrathoracic pressure during labor most probably accompanied by lowered pressure with increased blood and lymph flow following pains and after delivery? This, if true, would partially account for an exacerbation of a latent pulmonary tuberculosis or spread of an active process.

3. Might not the frequent and extreme intrathoracic pressure changes so traumatize the pulmonary scar tissue as to permit a reactivation or spread of tuberculosis?

4. Does not the increase in intrathoracic pressure with the consequent change in the circulation during violent exertion account for some sudden deaths in heart disease?

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## BOOK REVIEWS AND NOTICES

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**THE AUTONOMIC NERVOUS SYSTEM.** By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-Anatomy in St. Louis University School of Medicine. Pp. 697; 73 illustrations. Second edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$7.50.

Few parts of the body have been as much neglected in the average medical curriculum as the autonomic nervous system. It is a healthy sign, then, that this important work should require a new edition in the short space of 4 years. For the present edition, which combines even more than the first the anatomic, physiologic, pathologic and clinical aspects, the high praise of our former review (*AM. J. MED. SCI.*, 179, 842, 1930) can only be emphasized. "No student or physician can afford to do without it."

E. K.

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**RULES FOR RECOVERY FROM PULMONARY TUBERCULOSIS.** A Layman's Handbook of Treatment. By LAWRASON BROWN, M.D., Saranac Lake, N. Y. Pp. 275. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$1.75.

THE steady demand for this little book, from both patient and physician, has made it a recognized piece of equipment, to be kept in repair and modernized like any other device in the campaign against tuberculosis. Dr. Brown has given Education parity with Rest, Good Food and Fresh Air in this campaign, and brought the subject up to date. The sixth edition has all the merit of previous editions and includes new chapters on the surgical treatment of tuberculosis and convalescence. These chapters, from this authoritative hand, will serve to answer the many questions arising in patients' minds on the new forms of treatment.

E. L.

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**INTERNAL MEDICINE.** Its Theory and Practice. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1288; 35 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, \$10.00.

In his review of the first edition the Reviewer ventured to predict that this volume would take its place as a standard text in American literature. The appearance of a second edition within less than 2 years of the first seems amply to confirm this view. There are twenty-six contributors, all holding professorial appointments in medical schools. The subject matter has been thoroughly revised and new material has been added, including diseases of the lymphatic vessels, tuberculosis of the kidneys and urinary tract, a section on the classification of arthropods involved in disease transmission, and additional material on bacillary dysentery. Dr. Musser is to be congratulated on the excellence of his text-book.

R. K.

**CATARACT. ITS ETIOLOGY AND TREATMENT.** By CLYDE A. CLAPP, M.D., F.A.C.S., Associate Professor of Ophthalmology, Johns Hopkins University; Professor of Ophthalmology, University of Maryland, etc. Pp. 254; 92 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$4.00.

THIS excellent text covers much more than its title indicates. It is not only a review of our knowledge of the various forms of cataract but includes also other pathologic conditions of the lens, such as the congenital anomalies and dislocation. Following two chapters on the development and comparative anatomy of the lens, by Ida Mann, are chapters on the anatomy, physiology and chemistry of the normal and pathologic lens. The various theories of the pathogenesis of cataract are discussed and the various methods for the removal of cataracts are adequately presented. It is a highly commendable monograph.

F. A.

**HUMAN STERILITY. Causation, Diagnosis and Treatment.** By SAMUEL RAYNOR MEAKER, M.D., Professor of Gynecology, Boston University School of Medicine; Gynecologist, Massachusetts Memorial Hospitals, etc. Pp. 276; 27 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, \$4.00.

THIS manual is one of a series of publications sponsored by the National Committee on Maternal Health. The author offers as his apologia the need for assembling the established facts on the subject, as well as to offer a manual of clinical procedure based upon a large series of cases studied by the group method. In the study group a gynecologist, a urologist, an endocrinologic diagnostician and an internist were included. The collaborators have contributed special chapters relating to their particular fields. Beginning with the nine normal standards of absolute fertility the authors reverse them in the causative factors of infertility and upon this basis the text is developed in an exhaustive discussion of both the male and female factors.

The incidence and distribution of causative factors in a series of 100 infertile couples are tabulated. It is interesting to note that pituitary dysfunction ranked highest in both male and female constitutional factors, 33 and 26 respectively, and that thyroid conditions accounted for 21 factors in the male but only 6 in the female, while protein starvation, which the author, in discussing diet, states is the most marked dietary fault, accounted for 13 factors in the male and 20 in the female.

In addition to the history and physical examination the galactose tolerance test was used to determine pituitary disease. In the local factors, chronic prostatovesiculitis (18 cases) was most frequent in the male; while hypoplasia (42 cases), tubal occlusion (38 cases) and viscosity of endocervical secretions (31 cases) were the most frequent findings in the female.

The various procedures used, the technique, the results, the interpretations of the findings and the treatment of abnormal conditions is exceptionally well presented. The working schedule of the group practice is fully presented with sample charts. The concluding chapter deals with the prevention of involuntary sterility. This manual is a very thorough presentation of the subject and will be of undoubted value to those working in this field.

P. W.

**HYGIENE FOR FRESHMEN.** By ALFRED WORCESTER, A.M., M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 151. Springfield, Ill.: Charles C Thomas, 1934. Price, \$1.50.

THERE has been a great need for a hygiene textbook that is concise and yet accurately and clearly covers the fundamentals that should be

taught college freshmen. The author seems to have met these requirements fairly well in this short, inexpensive book. The introduction interestingly points out the importance of a knowledge of hygiene for college men. The chapters cover Biology, Nutrition, Digestion, Muscles, Nerves, Mental Hygiene, Reproduction, Disease Prevention and Immunity. The index is complete, but the glossary is rather short, listing only 28 words. There are no illustrations nor is there a list of books for collateral or advanced reading, which appear especially necessary for most elementary texts. On the whole the book is well written and covers the subject as thoroughly as possible in so short a course. It is recommended as a textbook for college freshmen taking a hygiene course consisting of a weekly lecture for one-half year.

N. B.

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LINCOLN'S NEW SALEM. By BENJAMIN P. THOMAS. Pp. 128; illustrated. Springfield, Ill.: The Abraham Lincoln Association, 1934. Price, \$1.00.

ASIDE from the interest attaching to this picture of the early stages of Lincoln's gradual development and the important favorable influence that New Salem had in shaping our "greatest American," this little book has a special message to medical men in portraying the village's two doctors and the characteristic medical practice in a pioneer community of our Middle West. In 1831, the month before Lincoln came to New Salem as a flatboat hand, arrived John Allen, a graduate of Dartmouth Medical School, only two years after the town had been planned and laid out. The next year came Francis Regnier who, with Dr. Allen, figured prominently in the intellectual life of the community (see illustrations of their log cabin living rooms and offices). Malaria, typhoid and smallpox were endemic with not infrequent epidemics of cholera. As usual they "purged, bled, blistered, puked and salivated," but faith doctoring and primitive magic doubtless had a more numerous following. In the town reconstruction that is now fortunately progressing, the two doctors' houses have already been included.

E. K.

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CLINICAL TOXICOLOGY. Modern Methods in the Diagnosis and Treatment of Poisoning. By ERICH LESCHKE, Professor of Internal Medicine in the University of Berlin. Translated by C. P. STEWART, M.Sc., Ph.D., Lecturer in General Biochemistry, University of Edinburgh; Senior Biochemist, Edinburgh Royal Infirmary; and O. DORRER, Ph.D., Research Assistant to Professor Wieland, Munich. Pp. 346; 25 illustrations. Baltimore: William Wood & Co., 1934. Price, \$5.

THIS compact statement by a well-known German clinician was written for the practising physician from the physician's standpoint. It is thus an adjunct to, not an inadequate rival of, the larger text-books written by pharmacologists. With the increasing frequency of industrial poisoning and suicide, the book is of timely interest and value.

E. K.

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JÖNS JACOB BERZELIUS. Autobiographical Notes Published by The Royal Swedish Academy of Sciences. Through H. C. SÖDERBAUM. Translated from the Swedish by OLOF LARSELL, Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 194; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, \$2.50.

IF medical readers require special inducement for reading this interesting autobiography of one of the greatest of 19th century chemists, it can be

supplied from consideration of his many medical contacts. First, a student of medicine and chemistry under Afzelius, he was later assistant physician at the Spa Medevi, where he published his first work on an analysis of these waters. Soon after receiving the M.D. degree, he was made adjunct and later full professor of medicine and pharmacy at Stockholm, where he was one of the founders of the Swedish Medical Society.

In these diary-like notes, now first translated into English, one will learn less about his numerous and important achievements than about the circumstances of his daily existence and the backgrounds of his period. His chemical discoveries are easily ascertained elsewhere, but here only we can learn of his minor achievements and vexations, his quarrels with Davy and Young, his honors and his failures, all told in a pleasantly naive style that has been retained by the translator. The book is a worthy successor to the preceding publications by this Society. E. K.

PARASITISM AND DISEASE. By THEOBALD SMITH, Director Emeritus of the Department of Animal Pathology, Rockefeller Institute for Medical Research. Pp. 196. Princeton, N. J.: Princeton University Press, 1934, on the Louis Clark Vanuxem Foundation. Price, \$2.00.

THIS book is developed about the principle that "parasitism may be regarded, not as a pathological manifestation, but as a normal condition having its roots in the interdependence of all living organisms." The many diverse relations between host and parasite are harmonized by the hypothesis that, for both parasite and host, two factors, one of offense and one of defense, operate to maintain equilibrium. It is indeed fortunate that one who has been so intimately and richly associated with the development of parasitology has given us this discussion of the biology of parasitism.

H. R.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOLUME X, MONOGRAPH XVI, PART II, INFLUENZA. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 916; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, \$17.50.

PART I of this monograph deal exhaustively with the part played by the various bacteria found in influenza; Part II takes up in a systematic and thorough manner the Complications and Sequelæ, Bacteriology of Influenzal Pneumonia and its Pathology. There are chapters on the Epidemiology and Modes of Possible Transmission, and 150 pages on Prophylaxis, Preventive Measures and Treatment.

In their own summary the authors state, "From the mass of evidence upon the subject it must now be assumed that Pfeiffer's bacillus *per se* is not the prime infective agent in influenza" (p. 1358). From a study of the work of Smith, Andrews and Laidlaw (Lancet, 2, 66, 1933), they feel that "as this work appears to have been most carefully controlled, the results are strongly conclusive that a virus is the primary cause of influenza." The virus appears "to act primarily as an intensely toxic irritant, producing a profound toxemia" and "hyaline necrosis of the terminal bronchiolar and alveolar walls, causing a rapid and profuse outpouring of serum and red blood cells in numerous patchy areas throughout the lungs" (pp. 1077 and 1366).



Sodium ricinoleate, as a preventive measure and for the local treatment of nasal colds and influenza in the earliest stages, was found to be the most efficacious remedy tried (p. 1261). The authors state that "vaccines are of value in the treatment of the respiratory complications of influenza and that successful results have been recorded not only in prevention, but in the treatment of influenzal pneumonia" (p. 1229). "The employment of convalescent influenza serum in the serum prevention of influenza certainly deserves a trial" (p. 1372) and although the results of such treatment in influenzal pneumonia are at variance, "there is evidence to indicate that this method if used early and given in sufficiently large amounts would appear to have a specific effect" (p. 1239).

The monograph contains 4500 references to foreign and American literature from which whole pages of verbatim quotations are transposed. While repeated reference to the same report at times becomes monotonous this is more than compensated for by the wealth of material it contains. The general format of the monograph maintains the excellence of the previous volumes, but it is regrettable that no photographs of the pathology of influenza were included.

J. C.

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BENJAMIN RUSH. Physician and Citizen (1746-1813). By NATHAN G. GOODMAN. Pp. 421; illustrated. Philadelphia: University of Pennsylvania Press, 1934. Price, \$4.00.

THAT such an important, versatile and interesting figure as Benjamin Rush should have waited 121 years for his biography is indeed strange; that it should eventually have been so efficiently set down is a matter for general satisfaction. The author's four years of study on an unusually rich source of material, especially at the Library Company's Ridgway branch (founded by Rush's son, James) has produced not only a scholarly, authoritative, well documented biography of "an important figure in our nation's past," but also an interesting narrative adequately enriched with sidelights from one of the most colorful periods of our history.

Very properly more than half the book is devoted to Rush's medical career, for "it is upon his fame as a physician that Rush's immortality will rest." Description of his 5 year, mutually satisfactory apprenticeship with Redman, attendance at Shippen's anatomy lectures (the seed that developed into the country's first medical school), his graduation at Edinburgh, studies in London and Paris, and subsequent successful practice in Philadelphia introduces the reader to a remarkably intelligent discussion of Rush's Cullenian theories of disease, of his heroic behavior in the yellow fever epidemics and of his reasons for his plan of excessive purging and bleeding. One misses—on first reading at least—the Sampson anecdote, his pet name for his favored drug calomel, because, so his detractors said, it had killed its thousands. Likewise one misses Holmes' tart completion of Rush's avowal that while medicine had been his wife, Science had been his mistress. Holmes, it will be remembered, allowed that it would have been better for all concerned if he had devoted more of his time to the legitimate object of his affections! Nevertheless, his contributions to medical science were considerable: while his chance observation that mosquitoes were more numerous in yellow fever years deserves little praise, the opposite is true of his original description of dengue, of his masterly observations on the nature and treatment of mental diseases, and of his correlation of distant disease with focal infection of the teeth. The importance of this latter concept has only been recognized within recent years. Rush's account of the 1793 epidemic of yellow fever won him international fame. After nearly a half century of intense activity, during which time he taught more than

3000 students, Rush was generally recognized as the leading medical authority and teacher of the country, "the Sydenham of America."

To many the account of his non-medical activities may be of greater interest. A philanthropist, whose actions followed close on the heels of thought, Rush early became a defendant of colonial rights. Inspirer of Thomas Paine's important pamphlet, "Common Sense," writer of many himself, Member of the Continental Congress, Signer of the Declaration (the only Doctor of Medicine but not the only physician who signed), Rush's position as a patriot is ensured. His medical services in the Revolution were also important, though from his bitter quarrel with Shippen, the Director General, he emerged unsuccessfully and at least not without blame. In this, as in the much discussed quarrel with Washington, Goodman believes that Rush, though impulsive and tactless, was inspired by good motives, and had much evidence to support his stand. Though elsewhere outspoken in criticisms of Washington, he foolishly (not cowardly) stooped to anonymity in a personal attack. Though a friend of Mifflin and Conway, there is no evidence, in Goodman's opinion, to show that Rush was implicated in the Conway Cabal. Non-controversial were Rush's activities toward freeing the negro, abolishing the death penalty and restricting the abuse of alcohol and tobacco. Founder of the first free dispensary, of Dickinson College, and one of the founders of our College of Physicians, a man of intense feeling and prompt action, Rush offers a splendid though difficult opportunity to the biographer. That Dr. Goodman has performed his task ably will be apparent to the reader. The University of Pennsylvania Press, too, is to be congratulated on sponsoring this work which deserves widespread popularity.

E. K.

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**THE COMPLEAT PEDIATRICIAN.** Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital. Unpaged. Durham, N. C.: Duke University Press, 1934. Price, \$3.75.

Not long since, the scientific world was jostled and then mildly amused at suggestions for the replacement of scientific journal articles by minute scrolls, kept in a central office, which could be sent out on demand and read under a magnifying glass. Similar thoughts are suggested by the fine print and modernistic condensations of the "Compleat Pediatrician." From a pleasantly pseudoantique title page, one passes through a conventional preface to a complexity of type changes, cross-reference numbers, symbols and abbreviations that demand a fortitude that many readers will not produce. However, once the method is comprehended and sufficiently practised, one suspects that the author's hope has been accomplished, namely, to produce a complete "ready reminder" of pediatric symptoms and signs, with alphabetically arranged diseases (diagnosis and treatment) sufficiently small "to be carried, like a stethoscope, in a physician's pocket or bag." (For suggested contents of said bag, see Appendix C.)

E. K.

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**SEX-HYGIENE.** What to Teach and How to Teach It. By ALFRED WORCESTER, A.M., M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 134. Springfield, Ill.: Charles C Thomas, 1934. Price, \$2.50.

THE proper teaching of sex-hygiene is a difficult problem. Most books discuss the anatomy and physiology of the sexual apparatus and elaborate on the venereal diseases, stressing their frequency and horrible consequences.

Many teachers agree that this is not the best method of approaching the subject; that the sex urge is too great to be overcome by mere fear of the venereal diseases. This is well borne out by the morality of many medical students and doctors, who, above all others, should be well acquainted with the medical aspect of sex. There remains only one course to pursue: an attempt to educate character by appealing to the morals of the individual.

Doctor Worcester has shown us an admirable way of handling sex problems of his concept of "the physiological basis for sexual morality as our trusteeship of the germ plasm." We are also made to see that the so-called sex urge is really a "parental urge and is the underlying motive in all that is loveliest in our lives." These principles, together with a gentle reminder of the doctrine of the great kinship of all mankind, constitute the substance of the text. The book consists of a collection of addresses delivered by the author before medical, religious and lay groups of both sexes. There is very little mention of the anatomy and physiology of the reproductive system and the usual somewhat morbid anatomic drawings are fortunately lacking. The venereal diseases and abnormal sex habits are sufficiently covered. The book contains much of value not only for the patient and student but for the physician and nurse as well. It is one of the best presentations of sex-hygiene that has been seen for some time and is well worth recommending.

N. B.

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**APPLIED ANATOMY.** By GWILYM G. DAVIS, M.D., Late Professor of Orthopedic Surgery and Associate Professor of Applied Anatomy in the University of Pennsylvania. Pp. 717; 674 illustrations. Ninth Edition reset, reillustrated and completely revised by GEORGE P. MULLER, M.D., Professor of Clinical Surgery, Graduate School of Medicine, University of Pennsylvania; Surgeon to the Misericordia and Lankenau Hospitals. Assisted by Drs. B. J. ALPERS, R. A. KIMBROUGH, JR., S. W. MOORHEAD, I. S. RAVDIN and S. D. WEEDE. Philadelphia: J. B. Lippincott Company, 1934. Price, \$9.00.

THE appearance of a ninth edition of this work is a real testimony of its merit. The book has been reset, and completely revised by Dr. Muller, assisted in the chapters on neurology by Dr. Alpers, on gynecology by Dr. Kimbrough, on urology by Dr. Moorhead, on the abdomen by Dr. Ravdin and in those on the extremities by Dr. Weeder. It has largely retained its previous form, discussing the regional anatomy and pointing out the applications of anatomical facts in surgical procedures. The excellent illustrations by E. F. Faber are scattered profusely throughout the book. The text has been brought up to date in practically every particular, although the Reviewer looked in vain for some discussion of the sympathetic nervous system, which has risen to considerable prominence in the past few years. This reliable guide to regional anatomy should find a prominent place in the libraries of all surgeons.

L. F.

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**STUDIES IN BLOOD FORMATION.** By T. D. POWER, M.D., M.R.C.P., D.P.H., D.P.M., Deputy Medical Superintendent, Brentwood Mental Hospital. Pp. 124; 25 illustrations. London: J. & A. Churchill, Ltd., 1934. Price, 8s. 6d.

THE author, primarily concerned with the study of insanity, began these investigations in order to elucidate mechanisms that have been used in the treatment of the insane. They are to be commended as carefully planned and executed and well controlled. Some statements or deductions to which one takes exception may pardonably be ascribed to a presumably short acquaintance with hematology. Thus the description of the Schilling

method is far from adequate; the deductions (probably incorrect) about amitotic budding and that granulocytes in the artificially produced leukocytoses do not go through the myeloblast stage fail to take into account the limitations of the fixed tissue method; and so on. Such important matters as the need for repeated rather than single counts, and for taking bone marrow specimens at several levels, on the other hand, get timely emphasis. Especially interesting are the demonstrations that sulfosin leukocytosis is due to newly formed cells; that thyroxin stimulates erythropoiesis and hastens differentiation and that therapeutic malaria produces a macrocytic anemia, both hemolytic and aplastic in type. E. K.

**THE DOCTOR IN HISTORY.** By HOWARD W. HAGGARD, Associate Professor of Applied Physiology in Yale University. Pp. 408; illustrated. New Haven: Yale University Press, 1934. Price, \$3.75.

WITH the increasing interest of the general public in the behavior of their bodies in health and disease, there has lately arisen a considerable group of books on various popularized aspects of medicine, of which the author's *Devils, Drugs and Doctors* is a prominent example. The present book tells in the same vivid, entertaining manner the story of medicine as seen through the lives and achievements of some of its principal exponents. From the anonymous Cro-Magnon witch doctor depicted in his ceremonial dress down through the ages to Gorgas of Panama Canal fame, the story unrolls with a compelling interest and yet without the inaccuracy that one often finds in such works. The illustrations are, especially for a University Press, poorly reproduced; their subjects and arrangement, too, are below the average that the book maintains. Especially interesting are the chapters of historical importance, such as those on the Black Death and the Mental Contagions. For many more than the author's children, for whom the book was written, should this "history of health" afford entertaining instruction. E. K.

## NEW BOOKS.

*Amebiasis and Amebic Dysentery.* By CHARLES F. CRAIG, M.D., M.A. (HON. YALE), F.A.C.P., F.A.C.S., Colonel, United States Army, Retired, D.S.M., Professor of Tropical Medicine and Head of the Department of Tropical Medicine, School of Medicine, Tulane University of Louisiana, New Orleans, etc. Pp. 315; 54 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$5.00.

*Manual of Clinical Laboratory Methods.* By PAULINE S. DIMMITT, Ph.G., Medical Technologist for the Stout Clinic, Sherman, Texas, etc. Pp. 156; 36 illustrations, including 7 colored plates. Philadelphia: F. A. Davis Company, 1934. Price, \$2.00.

*American Medicine.* By DR. HENRY E. SIGERIST, The William H. Welch Professor of the History of Medicine, The Johns Hopkins University. Translated by HILDEGARD NAGEL. Pp. 316; illustrated. New York: W. W. Norton & Co., Inc., 1934. Price, \$4.00.

*The Heart Visible.* A Clinical Study in Cardiovascular Roentgenology in Health and Disease. By J. POLEVSKI, M.D., Attending Physician and Cardiologist, Newark Beth Israel Hospital. Pp. 207; 122 illustrations. Philadelphia: F. A. Davis Company, 1934. Price, \$5.00.

*Hormone und innere Sekretion.* (Band 19 of Wissenschaftliche Forschungsberichte, Naturwissenschaftliche Reihe, Herausgegeben von Dr. Raphael Ed. Liesegang, Frankfurt a. M.) By DR. FRITZ LAQUER, Wuppertal-Elberfeld, Professor an der Universität Frankfurt. Pp. 368. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 18.

*To Remind—A Biological Essay.* (The Abraham Flexner Lectures, Series No. 2.) By SIR WILLIAM BATE HARDY, M.A. (CANTAB.), F.R.S., HON. D.Sc. (OXON.), HON. LL.D. (ABERDEEN, EDINBURGH, BIRMINGHAM), Fellow of Gouville and Caius College; Director of Food Investigation, Department of Scientific Industrial Research, etc. Pp. 45. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, \$1.00.

*The Farm Chemurgic.* By WILLIAM J. HALE, PH.D., Research Consultant, The Dow Chemical Company. Pp. 201; 5 figures. Boston: The Stratford Company, 1934. (No price given.)

*Heredity and Disease.* By OTTO L. MOHR, M.D., Professor of Medicine, The Royal Frederiks University, Oslo. Pp. 253; 107 illustrations. New York: W. W. Norton & Co., Inc., 1934. Price, \$3.50.

*Verhandlungen der deutschen Gesellschaft für Kreislaufforschung.* Seventh Session. By PROFESSOR DR. EB. KOCH, Bad Nauheim. Pp. 326; 65 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 15.

*The Principles of Therapeutics.* (The Abraham Flexner Lectures, Series No. 3.) By FRANCIS RICHARD FRASER, M.A. (CANTAB.), M.D. (EDIN.), F.R.C.P. (LOND.), Professor of Medicine in the University of London. Pp. 135. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, \$2.00.

*Erbpathologie, Ein Lehrbuch für Ärzte.* (Band 18 of Medizinische Praxis, Sammlung für ärztliche Fortbildung. Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme, Prof. Dr. K. Warnekros.) By Dr. O. FREIHERR VON VERSCHUER, Ausserordentlicher Professor der Universität Berlin und Abteilungsleiter am Kaiser-Wilhelm-Institut für Anthropologie, menschliche Erblehre und Eugenik, Berlin-Dahlem. Pp. 213; 32 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 8.

*Clinical Pathology of the Jaws.* By KURT H. THOMA, D.M.D., Charles A. Brackett Professor of Oral Pathology in Harvard University; Oral Surgeon to the Brooks Hospital, etc. Pp. 643; 423 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$9.00.

*Mental Health.* Past, Present, and Future. (The Colver Lectures, 1932.) By ARTHUR HILER RUGGLES, M.D., Superintendent of Butler Hospital, Providence, R. I. Pp. 104. Baltimore: The Williams & Wilkins Company, 1934, for Brown University, Providence, R. I. Price, \$1.50.

*Benign, Encapsulated Tumors in the Lateral Ventricles of the Brain.* Diagnosis and Treatment. By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, Johns Hopkins University. Pp. 189; 83 illustrations, 2 tables. Baltimore: The Williams & Wilkins Company, 1934. Price, \$4.50.

*Tumors of the Female Pelvic Organs.* By JOE VINCENT MEIGS, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Surgeon to Out-Patients, Massachusetts General Hospital, etc. With a Foreword by ROBERT B. GREENOUGH, M.D., President-Elect of the American College of Surgeons, 1933-1934, etc. Pp. 533; 261 illustrations, some in colors, and 49 tables. New York: The Macmillan Company, 1934. Price, \$6.00.

*Fifty Years of Medicine and Surgery.* An Autobiographical Sketch. By DR. FRANKLIN H. MARTIN. Forewords by WILLIAM J. MAYO, M.D., Rochester, Minn., and GEORGE W. CRILE, Cleveland, Ohio. Pp. 449; illustrated. Chicago: Surgical Publishing Company, 1934. (Price not given.)

*Diättherapie der Lungentuberkulose.* By DR. MAX GERSON, Wien. Mit Röntgenbefunden und einem Röntgenkapitel von DOZENT DR. FELIX FLEISCHNER, Wien. Pp. 619; 154 illustrations. Leipzig: Franz Deuticke, 1934. Price, M. 36.

## NEW EDITIONS.

*The Science and Practice of Surgery.* By W. H. G. ROMANIS, M.A., M.B., M.Ch. (CANTAB.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Surgeon and Lecturer on Surgery, St. Thomas's Hospital, etc., and PHILIP H. MITCHINER, M.D., M.S. (LOND.), F.R.C.S. (ENG.), Honorary Surgeon to H. M. the King; Hunterian Professor, Royal College of Surgeons of England, etc. Pp. 1901; 758 illustrations. Fifth edition, Vol. 1, General Surgery; Vol. 2, Regional Surgery. Philadelphia: Lea & Febiger, 1934. Price, \$13.00.

Any text which can rapidly pass through five editions contains real merit. The present edition has been extensively revised. The treatment of peritonitis, fractures, burns and varicose veins has been brought up-to-date. In several particulars the Reviewer criticized the fourth edition (AM. J. MED. SCI., 186, 574, 1933) but is happy to state that these matters have been thoroughly revised and corrected. Without doubt this edition will receive a hearty welcome which it justly deserves. I. R.

*Gynecology.* By BROOKE M. ANSPACH, Professor of Gynecology, Jefferson Medical College. Pp. 832; 679 illustrations, including 10 in colors. Fifth edition, reillustrated, reset and completely revised by the author with the assistance of PHILIP F. WILLIAMS, M.D., Assistant Professor of Obstetrics, School of Medicine, University of Pennsylvania, and LEWIS C. SCHEFFEY, M.D., Assistant Professor of Gynecology, Jefferson Medical College. Philadelphia: J. B. Lippincott Company, 1934. Price, \$9.00.

The present edition has been extensively revised and entirely reset. Many chapters have been rewritten and a section devoted to endocrine disorders has been added. In its present form, this book continues to maintain its place as an outstanding textbook. F. B.

*Recent Advances in Allergy.* (Asthma, Hay-Fever, Eczema, Migraine, etc.) By GEORGE W. BRAY, M.B., CH.M. (SYDNEY), M.R.C.P. (LOND.), Physician in charge of Children's Department, Prince of Wales Hospital; Assistant Physician, Princess Elizabeth of York Hospital for Children; Clinical Assistant, Asthma Clinic, Guy's Hospital. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital, etc.; Chairman, Medical Advisory Committee, Asthma Research Council of Great Britain. Pp. 503; 106 illustrations, including 4 colored plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1934. Price, \$5.00.

With 70 additional pages of text and over 700 new references, the new edition of this fine work is highly recommended to students and practitioners as a well-rounded treatise on allergy. Its only disadvantage from an American standpoint is its lack of hay fever plant surveys for this country. R. K.

*Practical Surgery of the Abdominal and Pelvic Regions.* By JAMES WILLIAM KENNEDY, M.D., F.A.C.S., Surgeon-in-Chief to the Joseph Price Hospital, Philadelphia; Consulting Surgeon to the Norristown, Coatesville and Chambersburg Hospitals, etc. Pp. 861; 133 illustrations, some in color. Second edition. Philadelphia: F. A. Davis Company, 1934. Price, \$7.50.

The present edition reviews the surgical and gynecologic teaching and operative technique of the late Dr. Joseph Price. The author, his pupil, feels that the teaching, often debated as radical, has stood the test of time. Especial emphasis is laid upon widening the indications for vaginal hysterectomy; the principles of this operation are extensively illustrated. P. W.

*Physical Chemistry for Students of Biology and Medicine.* By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 214; 28 illustrations. Second edition (with laboratory directions). Springfield, Ill.: Charles C Thomas, 1934. Price, \$2.75.

In the new edition are added laboratory directions for students, as well as several new sections to the text. For review of first edition, see this Journal, 186, 131, 1933. M. McC.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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### RECENT STUDIES ON FAT METABOLISM.

IN reviewing the recent contributions to the study of fat metabolism one is impressed by the fact that although our knowledge in this important field remains in a chaotic state there are distinct evidences of a more complete understanding of the complex problem than in the past.

**Methods.** Improvement and modification of methods have been directed in a large part toward the use of small amounts of blood for analysis. Smith and Kirk<sup>1</sup> have combined and modified the technique of Bloor, Pelkin and Allen, and Stoddard and Drury, so that only 0.5 cc. of whole blood is necessary to determine the fatty acid content. Hot benzene extraction is used and titration is carried out with potassium alcoholate. Kirk, Page and Van Slyke<sup>2</sup> have presented a gasometric method for total lipoids, cholesterol (total and esterified), phosphatids, cephalin and total lipid N, in which lipoids are extracted by an adaptation of Bloor's alcohol ether technique. For total lipoids alone 0.2 cc. of plasma suffices; for the different fractions 0.3 cc. is necessary. Boyd<sup>3</sup> has assembled a group of micromethods evolved by Bloor and his associates and from these has devised a procedure whereby all lipoids known at present in plasma may be determined on a small amount of blood. He uses the oxidative methods because, since it is impossible to state by which method correct lipid values are most closely obtained, results by several methods could best be compared if each were based on the same principle. The oxidative procedure was the only one which could be applied to all lipoids known at present to be in blood plasma. Schoenheimer and Sperry<sup>4</sup> have developed a micromethod for free and combined cholesterol in which finger blood can be used. A small amount of serum or whole blood (0.2 cc.) is precipitated with digitonin followed by the application of a color reaction to the precipitate. Amounts of cholesterol from 0.02 to 0.15 mg. may be determined.

Schoenheimer<sup>5</sup> has succeeded in developing a method for the separation of unsaturated sterols from a mixture in which saturated sterols are present in large amounts. The technique makes it possible to

isolate and identify cholesterol from human feces and may open up to a greater extent alimentary and biliary studies in cholesterol.

Discovery of quick, simple and accurate methods of determining lipoidal substances in the blood will give impetus to clinical research in this field. That less cumbersome methods lead to more widespread use is evidenced thus far by the use of Rückert's lipokrit method.<sup>6,7</sup> The principle is the same as that in the Gerber milk-fat method. Simplicity and accuracy are claimed and results have been checked against more elaborate, time-consuming methods. Allen<sup>8</sup> has also described a similar quick fat method for plasma. It is accurate, he says, for comparative studies, but determinations of accuracy are not published. It is fast and simple, no filtrations nor extractions being necessary, and employs an alkali reagent, as used in a modified Babcock procedure. Allen recognizes the necessity for further study to establish the applicability of the method for absolute determinations.

In cholesterol estimations as well, need for speed and accuracy has prompted Kámlet<sup>9</sup> to publish a colorimetric method. It appears to be sufficiently accurate for routine clinical work. The Lieberman-Buchard reaction is employed but no heat extraction is necessary, the extraction being carried out on blood dried on filter paper for 2 hours at room temperature. The widest variation from the Bloor-Sackett method was 9 mg. per 100 cc. and the average difference 3.55 mgm. per 100 cc.

Estimation of variations in the quantity and quality of lipoids in the various blood fractions has added appreciably to our knowledge of fat metabolism. Boyd<sup>10</sup> has introduced a new field in his determinations of the lipoid content of the white blood cells, carried out in normal young women midway between menstrual periods. The lipoid content was four times as great as in normal plasma with marked variation in the percentage composition of the component lipoids. As compared to body tissues the white blood cells contain a relatively large proportion of cholesterol esters, which vary from 0 to 75% of the total. Boyd again brings forward the thought that active cells contain a high percentage of phospholipoid and little or no cholesterol esters, while inactive or degenerating cells possess a low content of phospholipoid and an increasingly high amount of cholesterol esters. His results show that those white cells containing the highest per cent of cholesterol ester had the lowest per cent of phospholipoid, suggesting inert cells. When the cholesterol ester content was low the phospholipoid values were elevated, suggesting increased activity. Judged by these standards these cells were in different stages of functional activity, yet by usual standards all appeared the same.

**Alimentary Lipemia.** The constancy of blood fat levels and the variations which occur in alimentary lipemia constitute an important chapter in fat metabolism. McEachern and Gilmour<sup>11</sup> have shown wide fluctuations in the 5-hour fasting blood cholesterol curve. They conclude that such variations render haphazard studies of blood cholesterol of doubtful value. In 1928 McClure and Huntsinger<sup>12</sup> found only insignificant changes. The experiences of Bruger and Somach<sup>13</sup> were similar to those of McClure and Huntsinger. Ingestion of food gave no appreciable effect. Bloor,<sup>14</sup> too, has shown that with constant dietary and environmental conditions the plasma lipid level, postabsorptive,



in dogs was satisfactorily constant for 2 years. However, with the ingestion of urea, blood cholesterol changes occur. The ingestion of water alone gives no variations outside of the normal range,<sup>15</sup> but with ingestion of urea the resulting high blood urea was associated with a diminished cholesterol content. Bruger and Poindexter could not account for these changes on the basis of water fluctuation in the blood and made the assumption that the increment in blood urea modifies the plasma colloid structure so that cholesterol tends to decrease appreciably.

Alimentary lipemia, the rise of blood lipoids following the ingestion of fats, has been used to study the effect of certain drugs and hormones upon fat metabolism, a study which is comparable to the use of the glucose tolerance curve in carbohydrate metabolism.<sup>16</sup> Fat is absorbed from the intestine to the blood and from the blood to the tissues. Rony and Ching point out that the process is more complicated than is the carbohydrate curve, for it includes the rate of digestion of fat, which depends on bile and pancreatic secretion. They believe that with normal digestive organs under standard experimental conditions the rate of fat digestion and absorption is fairly uniform and that with this precaution in mind one may use alimentary lipemia curves as approximate measures of the rate of fat "utilization." Appreciating these difficulties in fat tolerance tests these authors showed in dogs that insulin promotes the passage of ingested fat from the blood stream into the tissues. This effect is independent from the effect of insulin on the blood sugar but does "show that deposition of ingested fat is in some way dependent on carbohydrate metabolism." Interesting in comparison with Rony and Ching's results are those of Sullivan and Cameron,<sup>7</sup> who, using the lipokrit technique, showed that the administration of adrenalin caused a lowering of increasing blood fats in the alimentary lipemia of diabetes. There are then two antagonistic hormones producing similar changes, a question which needs further consideration. Sullivan and Cameron interpret their results as evidence to support the view that adrenalin has a direct regulatory effect on fat metabolism. Raab<sup>17</sup> reports that pituitrin decreases the neutral fat content of the blood, a reaction abolished by paralysis of the centers in the tuber cinereum and by transection of the spinal cord. He concludes that pituitrin has an action on fat metabolism through a nervous pathway.

Chaikoff and his associates<sup>18</sup> found no typical or uniform responses of blood fatty acids in man by ingestion of a single fat. The atypical response is ascribed partially to previously uncontrolled diet and an insufficient time interval to establish a constant nutritional state. Other factors are important also. The authors contend that "the intestinal factors, as yet poorly understood, account in part, no doubt, for the normal variability in the response of the blood lipoids during the absorption of fat." While Rony and Ching contend, as already noted, that under standardized conditions alimentary lipemia curves serve as an index of the rate of fat utilization, these authors consider the uncertainty of rate of absorption as the fundamental weakness in such interpretations. They emphasize also that the variety of methods as well as the differences in the test meals used make difficult the comparison of results of different observers.

The work of Wilson and Hanner<sup>19</sup> on the character of the fatty acids with widely different dietary fats is extremely interesting. They determined the qualitative changes in the blood fat during alimentary lipemia by determinations of the iodine number on the serum following ingestion of 40% cream (iodine No. 30 to 40) and cod-liver oil (iodine No. 165). Calculations of the iodine number of the increment were between 39 and 60 in those fed the cream, and between 118 and 135 in those fed cod-liver oil. These results are interpreted in this light. After ingestion the neutral fat, resynthesized and present in the blood stream, is "largely or entirely composed of the fatty acids contained in the fat ingestion" and not a changed fat of a quality characteristic of the individual person.

**Blood Lipids in Thyroid Disease.** A greater understanding of changes in blood lipids in relationship to basal metabolism and thyroid disease is evident from recent work. The inverse relationship of blood cholesterol to the metabolism in thyroid disturbances is, of course, well known. In experimental animals<sup>20</sup> thyroxine injections have been shown to affect blood lipid levels raising them in whole blood determinations 20% to 80%. Liver phospholipids, however, have been found decreased when the basal metabolic rate is elevated by thyroxine.

That the blood cholesterol is specifically related to thyroid function and is independent of changes in basal metabolism except insofar as the change in basal metabolism is a manifestation of thyroid function, is becoming evident in the recent accumulation of data. In nephrosis,<sup>21</sup> for example, "although the total cholesterol is increased and the basal metabolic rate may be decreased there is no constant relationship between the two nor is there any predictable effect on thyroid therapy." In addition, more than a simple quantitative change in blood cholesterol occurs in cretinism. Besides the increase in cholesterol the ratio of esterified to free cholesterol may be changed and the relative proportions of each reversed. With therapy the normal relationship may again be restored. The same authors suggest that the determination of the free to ester cholesterol may be valuable in following the patient under such treatment.

Further evidence that thyroid function rather than the metabolic rate determines the state of blood cholesterol in thyroid disease, is evident from Hurxthal's<sup>22</sup> report. He states that subtotal thyroidectomy is sometimes followed by hypercholesterolemia without clinical myxedema, that the basal metabolic rate may be low postoperatively in the patient with respect to the blood cholesterol, and Roentgen ray therapy of the gland may produce hypercholesterolemia with or without clinical myxedema. Hurxthal<sup>23</sup> also showed that hypometabolism associated with suprarenal or pituitary insufficiency was not accompanied by hypercholesterolemia. He believes that hypometabolism found in these clinical conditions is not due to thyroid failure because of the absence of hypercholesterolemia. If in obesity a hypercholesterolemia is found, a concealed myxedema should be considered. In three definite conditions of endocrine dysfunction—hypothyroidism, Addison's disease and hypophyseal disease (chromophobe tumor)—the thyroid dysfunction alone raised the blood cholesterol over 200 mg. per 100 cc., strongly suggestive evidence that in other conditions the low metabolism is not due to secondary thyroid atrophy. It is further

evident from this work that changes in cholesterol content of the blood with changes in metabolism may be used as a differential point in diagnosis. Another strong link in the chain of evidence that blood cholesterol is independent of basal metabolic rate *per se* is the work of Cutting and his associates.<sup>24</sup> These investigators studied the changes in blood cholesterol after dinitrophenol medication. They reemphasize the fact that symptoms of hyperthyroidism may be divided into two groups, those resulting from the metabolic stimulation and those from stimulation of the sympathetic nervous system. The former are induced in dinitrophenol medication but not the latter. The results, too, tend to show that blood cholesterol is not controlled by the metabolic rate but rather by other thyroid secretory actions.

There is then, in cholesterol determinations, concrete evidence of the complexity of thyroid function as well as evidence that metabolism varies in endocrine disorders independently of thyroid function. A diagnostic weapon seems probable in the differentiation of those states associated with abnormal metabolism and a means of confirming those cases of supposed hyperthyroidism with normal metabolism and thyroid dysfunction varying independently of the metabolism.

**The Essential Fatty Acids.** Efforts to show that the body requires certain essential unsaturated fatty acids corresponding to the essential amino acids have been carried further. Evans and his associates,<sup>25</sup> working on rats, showed that normal reproduction without the essential unsaturated fatty acids is impossible. Their findings are striking. About 20% of the females failed to litter after implantation. Six per cent died during littering and in 95% of the pregnancies prolonged gestational periods resulted, displaying interference with the birth mechanism necessary to expel the young on the expected normal day. When littering took place it occurred with great difficulty. An unnatural chalky appearance of the corpus luteum was observed. Addition to the fat-free diet of the essential unsaturated fatty acids was the only factor which markedly improved the animals. Lactation on the fat-free diet was possible but not highly successful. The same authors<sup>26</sup> showed that the unsaturated and not the saturated fatty acids are the essential ones for rats. They call the essential unsaturated fatty acids vitamin F. Absence of these fatty acids is said to produce sterility in male rats.<sup>27</sup>

Hansen and Burr<sup>28</sup> discovered distinct differences in the serum lipoids of rats fed on fat-free and normal diets. Distinct differences were found in the iodine numbers of the two groups. Results<sup>29</sup> indicated that the serum fatty acids of rats fed on fat-free diets are less unsaturated than those of controls. The skin changes observed in rats suffering from the unsaturated fatty acid deficiency disease suggested to Hansen<sup>30</sup> that infantile eczema might be partially dependent on this type of dietary deficiency. Determination of the serum fatty acid in infantile eczema indicated less unsaturation than in controls. He<sup>31</sup> therefore gave oils rich in unsaturated fatty acids to 14 patients, with good clinical results. In 4 subjects followed with iodine numbers the numbers rose to normal figures parallel with improvement. The common use of crude coal tar in these lesions led the author to determine the effect of such therapy on the iodine number.<sup>32</sup> Results were similar to those with unsaturated fatty acids. The author emphasizes, however, that these reports are preliminary and the changes noted need further confirmation.

A further and distinctly separate attempt to relate lipid metabolism and eczema is the work of Faber and Roberts.<sup>33</sup> Blood lipoids were determined in patients with eczema and in normal controls. Outstanding differences occurred in the serum cholesterol. One-half of the cases showed a hypercholesterolemia. A few values were very low, so that the results were interpreted as demonstrating an instability in cholesterol metabolism. No differences in phospholipoids were noted.

**Blood Lipoids in Diabetes.** The lipid changes in diabetes have continued to hold the interest of many observers. Chaikoff, McGavack and Kaplan<sup>18</sup> determined the postabsorptive blood cholesterol in depancreatized dogs maintained on insulin and diet. They found a reduction in the ester cholesterol of the fasting blood in these animals. Curtis, Sheldon and Eckstein<sup>34</sup> quote Allen in stating that, aside from a good dietary supply of fat, the one prerequisite of diabetic lipemia is active severe glycosuria and hyperglycemia, and that in mild cases, or in severe cases which are controlled, the lipemia is never extreme in spite of high fat intake. Therefore, the diabetic lipemia represents more than a mere excess of fat in metabolism. Allen has never seen marked lipemia without acidosis. The findings of Curtis and his associates substantiate Allen's views that severe diabetes alleviated by treatment shows no extreme grade of lipemia. Unlike Allen, however, they found a parallelism between the degree of lipemia and degree of acidosis. Their results indicate that fat ingestion is unimportant in the lipemia if the fats are burned or stored and they believe that the lipemia is a result of almost total diabetes due to the disease itself or to a severe acidosis. In their case showing xanthomata a relationship between the tumors and the lipemia was apparent, for the xanthomata disappeared as the blood fats were reduced to normal levels.

Bruger and Mosenthal<sup>35</sup> also have attempted to determine the factors which control the plasma cholesterol level in diabetes, experiments which supplement those of the work already mentioned. On the injection of insulin, whereas a definite change occurs in the blood sugar, in cholesterol the value "may rise or fall but usually remains unchanged for several hours."

Man and Peters have added greatly to the understanding of lipemia in diabetes. In experiments in which transudation of fluid was produced, and by comparing the protein and lipoids in the serum and in pathologic exudates, they have shown that capillary walls are impermeable to cholesterol, phospholipoids and compounds of saturated and slightly unsaturated fatty acids, as well as to proteins.<sup>36</sup> With these facts as starting points they studied diabetic acidosis<sup>37</sup> to compare changes in lipemia with variations in the serum protein concentration, "for the double reason that not only are proteins indicative of the course of clinical improvement but also that hemoconcentration should produce marked differences in the plasma lipoids if normal capillaries are, as has been demonstrated, equally impermeable to protein and lipoids." Results bore out this reasoning. In acidosis the lipid fractions were above normal and returned on recovery to lower levels, following the serum proteins. Concentrations of cholesterol more nearly paralleled the proteins than did the other lipid fractions while contrary to usually accepted views the concentration of the serum fatty acids and cholesterol were not always related. Although variations in

the concentration of the lipoids of the blood depend largely on the degree of hemoconcentration other factors also may play a part. Hemoconcentration is offered as a possible explanation of the unexpected variations in cholesterol noted by Bruger and Somach.<sup>13</sup>

The relationship of cholesterol to obesity and degenerative diseases has been explored by Bruger and Poindexter.<sup>38</sup> Patients with diabetes, essential hypertension, osteoarthritis and arteriosclerosis were studied. The authors point out that the relationship between these diseases and obesity has been stressed for years; that the degenerative diseases, as contrasted to the inflammatory ones, are usually associated with increased blood cholesterol. Their results show that in 53 obese subjects without degenerative processes the plasma cholesterol was normal. However, in many instances when hypertension, diabetes or arteriosclerosis was associated, the cholesterol values were higher. The obese patients eating a diet high in fat had normal blood cholesterol levels unless the degenerative diseases supervened. They therefore conclude that the development of degenerative diseases in the obese is, as a rule, followed and not preceded by hypercholesterolemia and that the elevated cholesterol in the blood in these degenerative changes is usually to be regarded as a complication and not as an etiologic factor.

**Bile Salts in Fat Metabolism.** In Wright's<sup>39</sup> important experiments upon the biliary system of dogs, he finds cholesterol in bile in the free state only. He finds no esters of cholesterol in normal dog bile. With Whipple<sup>40</sup> he suggests a liver threshold of elimination of cholesterol. It was found possible to raise the blood cholesterol without a large increase in bile cholesterol and also to increase cholesterol elimination in the bile without change in the blood cholesterol concentration. Whereas the esters make up a large part of blood cholesterol they do not appear in dog bile, so that if the normal liver cell has a threshold for cholesterol it will not pass cholesterol esters. To this phase of the problem the authors offer further study. The factors influencing the appearance of cholesterol in the bile are considered, especially the dependence of the cholesterol of the bile on the circulation of the bile salts. The change wrought in the solubility of cholesterol in bile is not the only action of the bile salts, for the effect of bile salts on the liver cell itself is also important. The bile salts, in this conception, would act directly upon the liver cell, change its state, and permit the passage of cholesterol. The bile salts thus modify body function, the authors believe, not only in their "external sector" but also and probably with more importance in their "internal sector." Calculations show that a 10 kg. dog has in circulation 750 to 1500 mg. of cholesterol, from which only a very small amount, 10 to 20 mg., appears in the bile daily. This naturally points to the bile as an outlet for surplus cholesterol. However, since the increase in bile cholesterol is insignificant in dogs on diets rich in cholesterol, and since in liver injury due to chloroform both bile salt and cholesterol elimination are decreased in the bile, the bile cholesterol may also be related to the internal cholesterol metabolism going on in the liver cell. They point out a possible clinical application of these views, in that stasis of bile with high cholesterol values favors precipitation of cholesterol and subsequent formation of gall

stones. Not only would bile salts aid this situation by their cholagogue action but also by holding the cholesterol in solution in the bile.

Hawkins and Wright<sup>41</sup> stress the importance of only one variable, one type of injury, in observing changes in blood cholesterol. Using chloroform to produce such injury these observers showed that chronic derangements in liver function cause changes in plasma cholesterol metabolism. Chloroform by mouth decreased the ester cholesterol-cholesterol ratio, while bile duct obstruction raised the amounts of each but left the ratio unchanged. However, low blood cholesterol with dissociation of the esterified to total cholesterol ratio is not due to parenchymal liver injury only. While in biliary obstruction hypercholesterolemia results, if obstruction alone caused the change the free cholesterol of blood should increase much more than the esters with dissociation of the ratio. Experimentally a normal ratio is maintained. That the hypercholesterolemia in biliary obstruction cannot be due to changes in the liver alone is also evident.

Study of cholesterol-cholesterol ester has been proposed as a test to differentiate obstruction and parenchymatous lesions, for as noted in obstruction, the total cholesterol may be elevated with the ratio the same, while in parenchymatous injury the total cholesterol will decrease and the combined cholesterol drop markedly. While this may be true there are cases, as shown in dogs, where the blood cholesterol does not change. Also if the cholesterol is raised by obstruction, liver damage will cause a prompt fall, producing a weakness in the diagnostic index of cholesterol-cholesterol ester.

The authors, however, emphasize the significance of ratio of esterified to total cholesterol as a criterion of impairment of liver function over any change in total plasma cholesterol. While total cholesterol varies widely, the ratio is more constant even in dietary extremes. When values of the ratio fall below the low normal it is an indication of impairment of the functional capacity of the liver.

The studies of Wright and his associates are of extreme importance in laying the foundation of physiology of cholesterol metabolism upon which may be built knowledge of cholesterol pathology.

**Lipoid Changes in the Anemias.** The lipoid changes in the anemias have been investigated by Muller and Heath.<sup>42</sup> They point out that disturbances in cholesterol and lecithin metabolism frequently occur in anemia but that views in the literature are conflicting. Some say, for example, "that there is no characteristic difference in the blood lipoids in the different types of anemia and that the level of the blood cholesterol and degree of anemia are directly related—a general reaction to loss of cells and hemoglobin in the circulating blood." Muller and Heath believe from their results that whatever is the underlying cause of disturbed lipoid metabolism, anemia *per se* is not directly related to the level of the cholesterol and lecithin phosphorus in the blood. They have studied the cholesterol and lecithin values in various types of anemia. In pernicious anemia a definite relationship between the stage of the disease and blood lipoid was previously shown by Muller. The cholesterol and often the lecithin phosphorus decreased during a relapse, but as remission started a sudden rise in lipoids occurred with the reticulocyte response. However, in the anemia of chronic blood loss the low values did not vary directly with the reticulocytes in

therapy, nor were any relationships to reticulocytes or concentration of hemoglobin or red blood cells found in idiopathic hypochromic anemia. In acute blood loss, they state, however, that as a rule the reticulocyte outpouring was accompanied by hypercholesterolemia and lecithinemia. In cancer of the stomach the low lipid level remained regardless of the level of the red blood cells, except where the anemia improved with iron therapy.

The differences in behavior of the lipoids in these various types of anemia have led these authors to the conclusions that the plasma lipid is not directly related to the concentration of red blood cells or hemoglobin. Even with responses to treatment the reactions vary. In chronic blood loss the increase following therapy starts after the reticulocyte response, while in pernicious anemia the response parallels the reticulocytes. The high values of lipoids in acute hemorrhage are not adequately explained. Since low values occur in more severe anemia the authors discount the claim that a lack of red blood cells or decreased oxidation may cause it. Other explanations offered are a sudden decrease in lipase and in metabolism of the lipoids, a sudden outpouring of fats faster than they can be disposed of or possibly in part through displacement of fat by blood forming tissue (Bloor), and a sudden decrease in proteins with compensation by lipoids to help maintain the colloid osmotic pressure (Fishberg). The lowering of the lipoids in chronic blood loss is also inadequately explained at present. Lipoid exhaustion and the possibility of low values because of increased functional activity of the reticulo-endothelial system are entertained. The possibilities of nutritional effects are dispelled in idiopathic hypochromic anemia by the fact that lipoids remained uninfluenced after the anemia improved markedly on iron and on adequate diet.

**Lipemia of Pregnancy.** The lipemia associated with pregnancy has been considered by Boyd.<sup>43</sup> He finds it very "similar in nature to the lipemia in diabetes, nephritis, chronic alcoholism and persistent hemorrhage. Neutral fat is first increased and later the phospholipoid and cholesterol follow, the increase of the latter two appearing entirely secondary to the neutral fat increase and probably represents some adjustment in the lipid balance of the body." The most popular theories of the nature of the lipid increase are reviewed. An endocrine theory with hormones affecting the blood lipid levels heads the list. Absorption of products of fetal metabolism, placental toxins, change in blood lipase and many others are mentioned chiefly to emphasize the fact that none has been sufficiently proved. Experimental work on rats is discounted since rats do not display hypercholesterolemia in pregnancy.

Studies in lipid metabolism in pregnancy, as well as outside pregnancy, must embrace determinations of lipoids in whole blood, plasma, and red blood cells because of changes which may be significant in these three fractions. Boyd has found that the lipemia of pregnancy is due almost entirely to increase in plasma lipoids. Since the red blood cells show only slight change, determinations on whole blood give little indication of where the changes are occurring. The neutral fat shows an increase in the first trimester, the cholesterol and phospholipoid in the second. "At term neutral fat is elevated the most (over 100%); phospholipoid and free cholesterol are elevated about one-fourth. The

ratio of phospholipoid to cholesterol and ester cholesterol to total cholesterol are but slightly altered." Boyd concludes that his results place the lipemia of pregnancy in the class of similar persistent lipemias, as diabetes and experimental anemias. He finds no change in the composition of the fatty acids the iodine numbers in the pregnant women being similar to those in the non-pregnant state.

The cholesterol values in nephritic toxemia and eclampsia are higher than in the non-pregnant woman but not different from normal pregnancy.<sup>44</sup>

**Xanthomata.** The association of xanthomata with derangements in fat metabolism has continued to interest investigators. Michael and Nicholas<sup>45</sup> in 3 cases of xanthoma multiplex and 5 of xanthelasma showed disturbances of fat metabolism manifested by an abnormal distribution of lipid constituents of the blood or by the results of fat tolerance tests. Chaikoff *et al.*<sup>18</sup> found increased lipoids in the blood of a case of xanthomatosis. This patient failed to show, as did the one of Wile, Eckstein and Curtis,<sup>46</sup> any disturbance of the capacity of the tissues to take up absorbed lipoids, pointing to the view that the increased blood lipoids are derived from fat having already been stored or by synthesis of fat.

A study<sup>47</sup> of the lipid content of tissues in a case of Schüller-Christian's disease demonstrates that while reported variations in lipid content of various organs in this disease are marked, lipoids in tissues showed no marked difference from those of normal individuals except in xanthomatous masses.

**Cholesterol in Nephritis.** Ashe and Bruger<sup>48</sup> reported the cholesterol content of the blood in patients with nephritis, and with nephritis with uremia to investigate the changes in cholesterol when uremia develops. Their results show that a low blood cholesterol in Bright's disease with uremia foretells death, while a high cholesterol carries a good prognosis for the uremia. These findings were in no way correlated with edema. There was some evidence of a reciprocal relationship between cholesterol and urea, but this relationship was offset at times by various compensatory factors making it difficult to determine such a relationship uniformly. While no definite evidence of a cause for this relationship could be detected the authors believe that the low cholesterol values are probably due to such factors as cachexia and anemia.

Maxwell,<sup>49</sup> in a study of plasma cholesterol in nephritis, reports findings directly at variance with those of Ashe and Bruger. In acute cases they found that the plasma cholesterol appeared to be roughly proportional to the edema. In the chronic types variations were very wide and they were unable to demonstrate any satisfactory relationship with the clinical course of the disease. They state that the plasma cholesterol is of little prognostic significance and that they found slight ground to suggest that "an increase in the plasma cholesterol in the absence of edema is an indication of a probable early termination of the case in uremia."

**Lipoid Metabolism in Neuropsychiatric Disorders.** Because of the high percentage of lipoids in brain tissues, attempts have been made to correlate the lipid values of the blood with various mental and nervous diseases. Hopkins<sup>50</sup> has determined the whole blood cholesterol in epilepsy. Ketogenic diets producing a fatty acid acidosis and a rise in blood cholesterol suggest that a fall in blood cholesterol may occur



during the active phases of epilepsy. Hopkins' results show that the whole blood cholesterol in epilepsy appears to be significant in indicating the direction in which physicochemical changes are taking place and that the values are slightly lower in epileptics than in normals with a greater 24-hour variation.

In manic depressive psychosis as well, Slight and Long<sup>51</sup> discovered distinct differences from normal. Iodin numbers were lower in depressed cases, indicating a greater proportion of saturated lipoids than in the normals. The authors also conclude that in certain manic depressive cases a disturbance in lipid metabolism occurs, as shown by the increased lipid content of the plasma.

Changes in lipid metabolism in schizophrenia have been shown by Looney and Childs,<sup>52</sup> who found a slight degree of depression of the cholesterol of the whole blood. They state, however, that "although the blood cholesterol values for a series of schizophrenics is somewhat lower than for normals, in a given patient the values cannot be used as an aid in diagnosis, since variability is so great and range so wide that no single determination can be taken as characteristic."

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## PEDIATRICS

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UNDER THE CHARGE OF

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### THE TREATMENT OF CHOREA.

ACCORDING to Garrison,<sup>1</sup> "Chorea (dancing mania) was probably the result of physical degeneracy plus fanatical religious enthusiasm, and acquired the name of St. Vitus dance from the processions of dancing patients in the Strassburg epidemic of 1418." Because the first scientific description was given by Sydenham<sup>2</sup> in his "Schedula Monitoria" (1686), the condition is called Sydenham's chorea.

For many years the disease was treated empirically by the use of arsenic in the form of Fowler's solution and by salicylates. The latter were given because rheumatism was so often seen in cases of chorea. Later this association aroused interest, and the occurrence together of chorea and rheumatism was studied first by the clinicians and later by the bacteriologists. During the early phases of these studies there was considerable doubt that the association was more than a frequent coincidence; but with the work of Poynton, Payne and others on the bacteriology of these conditions, the rôle of streptococci in both was demonstrated. It followed that the relationship between chorea and acute rheumatic fever was more than casual.

In 1909 the direct relationship between these two diseases had not been established. Such a great authority as Holt<sup>3</sup> wrote as follows: "With reference to the use of drugs, it is advisable to separate from other cases those in which the connection with rheumatism is very close. In the rheumatic cases, salicylate of soda is often efficient, while the drugs usually employed may be absolutely without effect. In a case recently under observation, arsenic had been continued for 2 weeks

without the slightest improvement, when the patient had an intercurrent attack of subacute rheumatism for which salicylate of soda in full doses was given, with the effect of controlling the choreic symptoms promptly and permanently. In the non-rheumatic cases, arsenic is almost universally admitted to be the most valuable remedy we possess. . . ." Kerley<sup>4</sup> in 1919 said: "By treating every case of chorea as though the disease were rheumatism, my results have been strikingly good. Not only is the child given the salicylates, but he is put on an antirheumatic diet. The tonsils should receive careful attention, and in repeated attacks enucleation should be practiced." This author under the heading of "Supplementary Treatment" described the first form of serologic treatment as originated by Goodman, who reported 30 cases of chorea treated by the autoserum method. After having the child lie in bed for 3 or 4 days or longer without any medication, Goodman withdrew from a vein 45 to 50 cc. of blood and rapidly centrifugalized it. The serum was then pipetted off and kept on ice. A lumbar puncture was performed in the usual manner. The fluid was withdrawn slowly and about 20 cc. of the fluid were collected. The serum was then heated to body temperature and very slowly injected into the spinal canal. He warned that such an injection should take from 10 to 15 minutes, and usually 15 to 18 cc. of the serum were used. The patient should retain the recumbent position for at least 1 hour after the injection. From 1 to 4 injections were given, but the interval was not stated. This rather cumbersome procedure, not devoid of danger, did not attain wide use, although Goodman's report showed results that seemed very satisfactory from the standpoint of cures, improvements and the low incidence of recurrences. Incidentally his standard of classifying his results was based on rather rigid requirements. Under cured, he grouped those cases in which all twitchings ceased within a week. Under markedly improved, he grouped those cases in which there was a cessation of all twitchings within 2 weeks. As slightly improved, he classified those where the twitching disappeared at the end of the third week, and as unimproved, those in whom the twitchings were still present during the fourth week.

Other bacteriologic products have been used but with no uniform success, and as a consequence they have not become popular. Mention will be made later of two more recent bacteriologic preparations for the therapy of chorea. Before considering these let us review the treatment of chorea and add several methods that have been recommended. At first there was Fowler's solution, given in small doses gradually increasing to the point of tolerance if necessary. Later salicylates were used either separately or in conjunction with Fowler's solution. Rest in bed, bromids, luminal and similar drugs were used to decrease nervous excitability and to promote absolute rest. With the definite association of rheumatism and cardiac involvement with chorea the indications for rest became more imperative.

Several methods of treatment will now be enumerated or described without regard to their chronologic position in the development of the therapy of chorea. None of these has gained popularity if the dearth of references in the literature may be taken as a criterion. The two exceptions among the newer methods are the nirvanol and typhoid vaccine methods of producing artificial fever. Gopeman<sup>5</sup> reported a

series of 44 chorea cases in children treated by means of reclining baths at skin temperature for considerable periods of immersion. He said: "The sedative effect, which it is the object of this treatment to produce, was generally manifest after about a week. . . ." All the cases responded well after periods of treatment varying from 8 to 12 weeks in the milder ones, and up to 5 months in the severer cases. A certain number of selected cases was treated in the same ward on more usual lines with various drugs, including nirvanol, at the same time that the hydrotherapy treatment was used. It was observed that these responded more quickly, but relapses were more common. The notes of 50 unselected cases treated on more orthodox lines were examined, and the incidence of relapses was compared with those occurring over 4 years in the presented series. In the former group where drugs were used, there were found to be 8 relapses, a ratio of 1 to 6; while in the present series there were 3 relapses or a ratio of 1 to 13.

Leopold and Rothstein,<sup>6</sup> using a ketogenic diet similar to that used for epilepsy in a series of 12 cases of chorea, noted good results in 9. They found that the period which elapsed before the development of a definitely marked ketosis varied from 3 to 8 days. The period of continued ketosis required for the disappearance of the choreiform manifestations was approximately 9 to 24 days. In 2 cases the authors were forced to discontinue the diet after several days before a definite ketosis was even produced, because of the development of acute endocarditis and pericarditis in 1 case, and the contracting of a severe lobar pneumonia in the other. In 1 case of severe chorea in a stout girl of 11 years, weighing 129 pounds, who had displayed marked symptoms of chorea for 7 months prior to her hospitalization, it was impossible to improve her condition. It was noted that although a definite ketosis was produced within 6 days, and the child was kept on the very low carbohydrate stage of the diet, receiving 10 gm. of carbohydrate per day, the production of a ketosis was not constant. Some days the ketosis would be moderate, whereas on others the tests for acetone and diacetic acid in the urine would be negative. Apparently the ketogenic diet may be used with success in most cases of chorea, according to these authors, except those which have acute respiratory or other infections such as a concurrent pneumonia. In some instances it was found that the high fat was not well tolerated, for nausea and vomiting would occur as signs of a fat intolerance without any clinical symptoms of an acidosis developing. In fact, according to weekly chemical examinations of the blood, no material or clinically significant changes in the blood or CO<sub>2</sub> figures occurred. If this condition were found true in a large series of cases, it would seem to show that the ketosis produced, as evidenced by the presence of acetone and diacetic acid in the urine, is not always accompanied by a clinically significant acidosis, such as might be expected to cause a material change in the carbon dioxide combining-power of the blood. The authors felt that the efficiency of the diet had not been proved sufficiently to warrant risking the possibility of causing gastro-intestinal upset in such cases that may have the complications mentioned before. Consequently in treating these children they recommended rest in bed, the use of sedatives and other symptomatic treatment. Whether the ketosis produced in the treatment of chorea will be of any value in the prevention of cardiac com-

plications, they were unable to say with the data at their disposal from the study of this series of cases. They thought, however, that the actual shortening of the duration of the chorea might diminish the possibility of such complications occurring. That the authors failed to be convinced of the efficiency of this treatment of chorea is suggested by the absence of further reports by them after several years. Doubtless it was used by many others anxious to discover a safe and efficient procedure in the handling of this disease, but no evidence of their experiences appears in the literature. Our own experience with the ketogenic diet in the treatment of severe cases was that improvement followed usually only after long periods extending to from 4 to 10 weeks. In some cases the maintaining of ketosis as evidenced by acetone and diacetic acid in the urine was difficult. Another disadvantage that this method has in common with most of the procedures so far recommended in the treatment of chorea is the necessity of hospitalization.

Speaking of the medicinal treatment of chorea, Mutsch<sup>7</sup> says that calcium acetylsalicylic acid or calcium aspirin possesses the means of dealing simultaneously with the three etiologic factors of chorea: rheumatism, nervous strain and calcium deficiency. This was the only mention of calcium deficiency as one of the etiologic factors in chorea that we found. According to him it supplies an adequate amount of calcium, produces a useful sedative effect on the brain and combats the rheumatic element if given in sufficient doses, readily dissolving in water and forming a neutral solution suitable for administration by vein or subcutaneously as well as by mouth. By crystallization from a solution of calcium chlorid, a form of calcium acetylsalicylic acid has been obtained with a stability approximately equal to that of the parent acetylsalicylic acid itself. The author's 19 patients were kept in bed. A light, mixed diet was given. The only drug employed except laxatives was calcium acetylsalicylic acid, dissolved in water and administered by mouth. The average daily dose varied up to gr. xlv for a child aged 12 years. The rapidity of response did not vary accurately with the original severity of the choreic movements, as mild cases sometimes proved to be more resistant than severe ones. The attack was not registered as over until the condition had so far improved that an average medical man would have had difficulty in diagnosing the case as one of chorea. Spontaneous movements would have stopped. Voluntary movements were of average accuracy, and the patient could sustain a steady grip of the hand for a minute or so without fluctuation. The average time taken to control chorea was 17 days and the limits were 7 to 46 days. The drug diminished the discomforts of the patients at all stages of the treatment, and did not produce any mental depression, undue drowsiness or digestive derangement. There were no relapses or secondary exhaustion when the drug was finally withdrawn.

Charney<sup>8</sup> and Williams<sup>9</sup> treated 2 and 4 cases respectively with J. C. Small's antiserum for *Streptococcus cardio-arthritis*. Small had reported favorable results with antiserum and vaccine and described a skin test for susceptibility. His articles on specificity and his results were convincing enough to induce many clinicians to use this serum, but few have reported their results. Swift has stated that this serum causes a non-specific reaction, similar to that obtained with any anti-

streptococcic serum. Charney, feeling that reports of unfavorable results are as essential as are favorable reports, described 2 cases of chorea, treated with the serum, one with apparently no result and the other with a reaction that appears to have led to the death of the patient. The cases were chosen as illustrating extremes of severity of the disease and because of the difference in the results.

"The Nirvanol Therapy of Chorea" was the subject of a paper by deRudder.<sup>10</sup> Nirvanol is a phenyl-ethyl-hydantoin that was introduced originally as a new sedative and was widely used as such. In 1919 Roeder reported good results obtained with nirvanol in the treatment of chorea minor, but observed that during the nirvanol medication a drug exanthem developed. Rietschel reported in 1920 on the basis of a study of cases that this drug exanthem was essential for the production of the therapeutic effect of nirvanol. Because of its unpleasant side effects the drug is no longer used as a sedative, but it is employed largely in the treatment of chorea. Nirvanol is indicated only in the treatment of the severest cases of chorea and its complications must be considered. It must be emphasized that the nirvanol treatment must not be looked upon as indifferent. In severe cases the use of this drug is definitely indicated. Because of the risks associated with the treatment, nirvanol medication is employed largely only in the hospital where the patient can be carefully watched by a competent physician. The effect of the drug is based on the appearance of the exanthem. In order to produce this a daily administration of the drug is necessary. If no reaction takes place after 14 days the use of the drug must be discarded since an exanthem could no longer be expected. The dose of the drug is generally 0.3 gm. per day and in older children it is occasionally used in doses of 0.6 gm. per day. This dose must under no conditions be exceeded. During the medication strict bed rest must be maintained. The "nirvanol disease" appears between the 6th and the 14th days. Around this time there develops a morbilliform exanthem frequently associated with fever. The degree of intensity of the exanthem varies. Occasionally there is also observed a slight irritation of the conjunctivæ. In rare cases the reaction may be severe. Rusleer observed a case with a severe recurrent exanthem, severe stomatitis, balanitis, and a very high fever. Jolozic observed a case of transitory intestinal paralysis with a high degree of tympanites following the use of excessive doses. These severe although rare cases show the great necessity of care when this treatment is employed. Its use is justified by the fact that chorea itself may result fatally. The success of the therapy and the appearance of the reaction is lightning-like and more or less certain. Of interest is the fact that occasionally shortly before the appearance of the reaction, a slight aggravation of the choreic twitchings may be observed. Regarding the biologic character of the nirvanol disease, it may be stated that it has some resemblance to an anaphylactic reaction. The incubation time of from 9 to 12 days may be considered as the time necessary for the development of amboceptors until then absent from the body. The clinical picture is identical with that of serum disease. There frequently develops an eosinophilia of a considerable degree. The metabolic-chemical changes are similar to those observed in serum disease. Shortly before the appearance of the reaction there develops an alka-

lotic change in the organs, a "pre-anaphylactic tetany" similar to that observed in serum disease. There also develops a galvanic hyperirritability of the peripheral nerves. As the exanthem develops there occurs a change in the metabolism in the direction of acidosis, and it seems that this type of "metabolic shock" is the most important factor in the nirvanol therapy.

Dennett,<sup>11</sup> who studied 93 cases of chorea treated with nirvanol, said, "One has to use the drug with caution—one must have brains as well as the drug." Marick,<sup>12</sup> presenting his experience in some 60 cases, feels that the nirvanol treatment of the chorea patient at home is safe and practical. This is contrary to the opinion of practically every other observer. Call<sup>13</sup> had 26 cases in his series. Silber and Epstein<sup>14</sup> studied 28 cases of chorea treated with nirvanol.

Freire<sup>15</sup> claimed that constant and excellent results were produced with febrifacient injections of Sufroge. The production of fever by a serologic product was described first by Sutton.<sup>16</sup> Her investigations were based on the hypothesis that the fever is the effective factor in the treatment which she described. She fully realized that this point was not proved and that other immunologic factors may be operative; but support is lent to this hypothesis by the fact that fever is common both to intoxication with drugs such as phenobarbital and phenylethyl-hydantoin, which may have a beneficial effect on the chorea, and to foreign protein therapy. In order to investigate this question, typhoid vaccine was given to most of the choreic children at Bellevue Hospital during parts of 1929 and 1930. This vaccine was chosen as a simple and safe means of producing fever. The object was to obtain fever for several days in succession. With plain typhoid vaccine, fever was not produced if the injections were given at intervals of less than 5 to 7 days, and not every case responded with high fever. Possibly if larger doses had been given, more sharp reactions would have occurred. However, enough cases showed marked improvement following a sharp febrile reaction to encourage a continuation of this line of treatment. In the fall of 1930 typhoid-paratyphoid vaccine was tried. This vaccine when given intravenously invariably produced a sharp febrile reaction, even when given every day. Up to the time of her report in May, 1931, Sutton had treated 24 cases of chorea with intravenous injections of this vaccine with encouraging results. It is possible that some other more satisfactory way of producing fever may be found, but this method is simple, safe and cheap. The progress of the chorea was used as a guide for the continuation of the treatment. Most cases seemed to require a febrile period of about a week, while others needed more, depending chiefly on the severity and duration of the attack. Except for rest in bed and general nursing care, no other treatment was employed in this series. When possible, the children were kept in small rooms off the ward; but a number were treated in cubicles in the ward with no attempt at special isolation and quiet. Codein was given in some cases for severe headache during the reaction. It is important to note that acetylsalicylic acid is contraindicated, since it reduces the temperature. The injection was usually given in the afternoon, so that the child would not miss his dinner. The reaction was over in time for him to have an undisturbed night's sleep. The effect of the fever on

the chorea was usually immediate. After the febrile reaction was over, the movement was noted after each reaction. Most of the children lost weight during the period of treatment and sometimes seemed worn out after it. For this reason they were kept in bed for a week after the treatment was stopped, in order that they might regain their strength before being allowed any activity. They were kept in the hospital for another week of observation while up and about the ward. High-caloric diets were given with extra milk, cod-liver oil and iron tonics when indicated. A few were given transfusions of whole blood for moderate secondary anemia. Such measures were designed to hasten convalescence. Occupational therapy was found to be helpful in keeping the children busy and happy. It was particularly helpful where there was incoördination due to muscular weakness, which often persists after the real chorea is over.

Dennett (*loc. cit.*), however, found that the reactions to typhoid vaccine in some patients were too severe to warrant its use, and he does not allow its use on his wards, preferring nirvanol in the treatment of this disease. Cheetham<sup>17</sup> presented several examples from his series of cases and concluded that the treatment of chorea by artificial pyrexia shortens the duration of the choreic movements, but does not prevent recurrences and does not appear to have a beneficial action on rheumatic carditis. In view of these conclusions it is clear that the method requires exhaustive trial before it can be generally adopted. Its grave danger lies in the tendency to produce a false impression of cure by abolishing the movements, which in themselves are merely a symptom, when serious changes may be occurring in the heart. A child with acute rheumatism should not be allowed out of bed as soon as the joint swellings have subsided under the influence of salicylates. In the same way it is undesirable to allow a child out of bed after the onset of an attack of chorea unless it can be conclusively proved that the treatment which cut short the choreic movements also cut short any accompanying carditis. When these facts are borne in mind it is clear that artificial pyrexia has a very limited place in the treatment of chorea according to the contention of Cheetham.

Walker,<sup>18</sup> Bateman<sup>19</sup> and Hoverson<sup>20</sup> are among those who have published favorable reports. Walker believed that since the good effects of the treatment depend on the fever produced, vaccine treatment would seem to have distinct advantages over phenyl-ethylhydantoin for all cases can be made to react immediately without waiting for a period of days for the toxic symptoms to develop, there are no complications, the results are as good or better and the amount necessary to obtain a satisfactory febrile reaction is under perfect control. Bateman said, "Most patients show a marked improvement after two or three treatments, and are usually free from choreic movements in a week." As might be expected the milder cases improve more quickly than the severe ones. Patients with a long history of chorea before admission to the hospital may be slow in their response to treatment, and it should be remembered that in those patients habit movements may be superimposed upon those that are essentially of choreic origin. At the end of the fever treatments the patients should be kept in bed for a few days and are then allowed up for a week before discharge



from the hospital. The usual length of time in the hospital is 3 weeks. This compares very favorably with the 7 weeks which most other methods require. Mention may be made of those cases of chorea which on admission to the hospital show a cardiac murmur of rheumatic origin. This need not be regarded as a contraindication to treatment, unless it is thought that the circulatory system cannot support the effects of a high fever. Walker feels that the treatment has proved satisfactory. It has considerably shortened the duration of the stay in the hospital and it is not accompanied, so far as is known at present, by complications. The patient's discomfort attendant upon the treatment is much less than might be expected, and it is probably preferable to the weeks in bed and the long continuance of choreiform movements associated with the other methods. Hoverson reported a series of 6 cases, 4 suffering from the Huntington's type of chorea and 2 cases of Sydenham's chorea that were treated by fever therapy which was induced by the intravenous injection of typhoid vaccine. In the cases of Sydenham's chorea, there was a complete recovery from the chorea. Regarding the more chronic chorea, 2 patients showed a recovery, 1 a temporary improvement, and 1 no change. He felt that fever therapy is of definite value both for the acute and the chronic forms of chorea.

Montfort,<sup>21</sup> in an attempt to clarify the present status of the treatment of chorea, made a comparative study of 49 patients, 24 of whom were treated with phenyl-ethyl-hydantoin and 25 with typhoid-paratyphoid vaccine. He found that there were spectacular benefits from phenyl-ethyl-hydantoin in some cases, but in the majority of cases the average duration of the disease was 24 days; in 8 cases the condition was unimproved; in 1 case the drug caused a fatality. There is justification, therefore, for characterizing this method as of questionable value. The results of treatment with typhoid-paratyphoid vaccine showed that this form of therapy was not dangerous, but that it produced obvious discomforts such as chills and fever during the febrile period. However, the duration of treatment with this method was shorter by 8 days than that with phenyl-ethyl-hydantoin. There were no recurrences of chorea in the patients treated with the typhoid-paratyphoid vaccine who were followed for one year, and it was noted that carditis, the most dangerous sequel of chorea, did not occur in those treated with this preparation during this period of observation. It is, of course, too soon to make any sweeping conclusions as to the advantages of treatment with typhoid-paratyphoid vaccine, but it would seem that this ought to be the treatment of choice. In Montfort's series of cases the time required to arrest the symptoms was from 2 to 3 days longer than in the patients in Sutton's series. Speculating as to the factor responsible for the improvement in these cases, one is impressed by the chemical changes taking place during the febrile period when the typhoid-paratyphoid vaccine is introduced. There was noted a change in the acid-base equilibrium. There was invariably a low carbon dioxide content of the blood during the prolonged fever, with a low level for chlorids, a moderate raising of the calcium level and a lowering of the phosphorus level. It was observed in 3 cases that the pH of the blood was slightly increased coincidentally with

the lowering of the carbon dioxid content. The question arises whether this sudden shift in the acid-base is operative in the improvement, or whether the improvement is due to the increase in calcium during the febrile period. Although there is a lowering of the carbon dioxid volume per cent and the chlorid level, there is an increase in pH. The bases are not lost, but are bound to the proteins, owing to the increase in pH. There is probably a sudden shift to alkalinity. Bischoff, Ullman, Hill and Long, discussing hyperthermia, confirmed the hypothesis that of all the changes taking place in the chemistry of the body following a gradual moderate rise in body temperature, the one of fundamental importance is the loss of CO<sub>2</sub>. This was pointed out previously by others. The data of this series illustrated this point very strikingly. The one effect which was the same in all of the experiments was the rise in the blood pH. This, in connection with other data, showed conclusively a lowered carbon dioxid tension of the blood. The other changes, which in some instances did not follow, were a result of the lowering of the carbon dioxid tension. Thus, the pH of the urine remained unchanged or decreased, the calcium was unchanged or increased, and the hemoglobin was more or less highly oxygenated. The change in the total CO<sub>2</sub> content of the blood was readily accounted for by the shift of the base to the blood protein due to the increase in pH. Since the alkali reserve of the blood remained the same or increased slightly, and since the pH of the urine as excreted was not more alkaline than the blood there is little reason for believing that the body was attempting to compensate for the lowered carbon dioxid tension by lowering the alkali reserve. Diminution of the blood pressure was also noted during the febrile period. The pulse pressure fell disproportionately more than the systolic pressure. Of the entire series, 17 patients treated with phenyl-ethyl-hydantoin and typhoid-paratyphoid vaccine showed evidence of carditis on admission; 23 of the entire series had had their tonsils removed, and 8 showed roentgenographic evidence of sinus and antral involvement. All of the patients treated with typhoid-paratyphoid vaccine gave a positive Widal reaction in all dilutions during their stay in the hospital. From these observations it may be concluded that typhoid-paratyphoid vaccine proved of greater value in the treatment of chorea than phenyl-ethyl-hydantoin because of its harmlessness, the shorter time required for cure, the probable arrest of recurrences, the ease of administration, the significant lack of sequelæ and the occurrence of chemical changes during the febrile period.

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 19, 1934

**An Analysis of the Spectra of Hemoglobin Derivatives.**—DAVID L. DRABKIN (Laboratory of Physiological Chemistry, University of Pennsylvania). A study of the absorption spectra in both the visible and ultra-violet regions of several hemoglobin derivatives has led to an analysis which heretofore has been applied only to the absorption spectra of very simple substances.

The complex absorption curves may be considered to represent summations of a number of individual bands. All the derivatives studied—oxyhemoglobin, carboxyhemoglobin, cyanhemoglobin and two forms of methemoglobin—have certain bands in common. The position of the peaks of these bands may be expressed by  $n = \frac{\nu \times 10^{-2}}{60}$ , where  $n$  represents a simple integer. In the regions of the spectra studied the values of  $n$  which have been obtained are 3, 4, 5, 6, and 7. These five bands therefore belong to a single series, the members of which are at equal frequency differences from each other. Such bands are probably produced by the same influence in the molecule, and are deduced to represent the general structure of hemoglobin.

The so-called  $\alpha$ -bands of oxyhemoglobin and carboxyhemoglobin do not belong to the above series and probably represent the union of hemoglobin with a gas. Such an analysis also suggests that hemoglobin may have absorption in the infra-red, where the first two members of the  $\frac{\nu \times 10^{-2}}{60}$  series may possibly be demonstrated.

**Observations on the Effects of an Arteriovenous Fistula on the Human Circulation.**—L. B. LAPLACE (Laboratory of Physiology, University of Pennsylvania). A case is described which presented a traumatic fistula between the left femoral artery and vein. The fistula had caused an enormous cardiac enlargement and advanced congestive failure. The cardiac output was decreased 20% on digital compression of the fistula and 24% after operation. The change in minute volume de-

pended chiefly on slowing of the heart rate rather than on change in stroke volume. Slowing of the heart rate on compression of the fistula was not directly proportional to the associated elevation of arterial pressure, indicating that other factors must be involved in the bradycardiac reaction. Despite the presence of the open fistula the arterial blood pressure, although low, was maintained within normal physiological limits. The skin temperature was elevated in both legs on compression of the fistula, indicating an increase in capillary blood flow when the leak was blocked. Following treatment the heart size returned to normal indicating that the enlargement was due to dilatation rather than hypertrophy. The dilatation appeared to depend, as Lewis and Drury believe, on a disproportion between the work of the heart and the coronary blood flow. Fluoroscopic examination demonstrated a prompt diminution in pulmonary blood volume on compression of the fistula. The effect of the fistula on respiration, venous pressure, oxygen consumption, pulse wave velocity, and the electrocardiogram are also described.

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**The Effects of Prolonged Exercise on the Weights of the Organs of the Albino Rat.**—HENRY H. DONALDSON (The Wistar Institute, University of Pennsylvania). The brain of the captive albino rat weighs 10 to 12% less than that of the wild Norway, from which it is derived. Continued exercise in the drum cage increased the brain weight of the albino by about 2%. When this form of exercise was continued for seven generations, the gain in the last generation was again about 2%. This modification is, therefore, not inherited.

Starting at 57 and ending at 182 days of age, the effect of such exercise on 14 other organs was determined on 26 males and 26 females. Each group ran 500 miles in 125 days. In the females all the organs and in the males all except the thyroid and thymus show increased weights. The increases are substantial except for the musculature, brain and cord. The final body weights were below those of the controls despite the fact that the male tests gained 5.9 gm. and the female tests 3.5 gm. from their heavier organs. The diminished body weights are credited to a loss of fat by the tests.

When rats are exercised for 90 days and then rested for 125 days, the organ weights of the tests are much nearer those of the controls. The deviations, therefore, do not persist. Exercise as here used produces accelerated growth; but during the subsequent resting period the organs of the tests grow less rapidly than those of the controls. It seems probable that a similar type of exercise would produce like changes in the organs of man.

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**The Effect of Oxygen in the Prevention of the Liver Necrosis Produced by Volatile Anesthetics.**—S. GOLDSCHMIDT, I. S. RAVDIN and BALDUIN LUCKÉ (Laboratories of Physiology, Research Surgery and Pathology, University of Pennsylvania). A comparison has been made of the relative incidence of liver necrosis in dogs anesthetized in a semiclosed system when the anesthetic was volatilized with air and when it was volatilized with oxygen. The data show that the use

of oxygen with either divinyl ether or chloroform is a potent factor in the reduction of postanesthetic liver necrosis.

When divinyl ether was used as the anesthetic by any method, liver necrosis was not observed with any degree of regularity until the anesthesia was maintained for a 3-hour period. The incidence of postanesthetic necrosis after 3 hours of anesthesia in a semi-closed system was nearly twice as high when the anesthetic was volatilized with air as with oxygen.

Chloroform anesthesia on the other hand resulted in a high incidence of liver necrosis in dogs after 1 hour of anesthesia. The incidence of liver necrosis following 1 hour of chloroform anesthesia in a semi-closed system was approximately ten times as great when the anesthetic was volatilized with air as with oxygen.

Liver degeneration has been produced in the dog following 3 hours of ether anesthesia when the anesthetic was volatilized with less than atmospheric pressure of oxygen, *i. e.*, oxygen 15% and nitrogen 85%.

Data demonstrating the efficiency of oxygen during anesthesia will be presented and the general implications of our findings will be discussed.

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### Correction.

In the article by L. F. Craver in the November, 1934, issue of this journal, on "Five-year Survival in Hodgkin's Disease," the percentage figure of survival of proven cases in the summary (p. 612), should be 12% and not 16.8%.

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ORIGINAL ARTICLES.

THE CHANGING CAUSE OF DEATH IN DIABETES MELLITUS.

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WITH the discovery of insulin, in 1922, the treatment of diabetes mellitus was placed upon a new basis. Fitz and Murphy,<sup>1</sup> of the Peter Bent Brigham Hospital, anticipating that the clinical picture and course of the disease might be changed to a considerable degree by the newer method of treatment, analyzed the records of all the cases of diabetes mellitus which had died in that institution between the time when it opened, in 1913, and the commencement of the insulin era, in 1923. Their conclusions may be summarized as follows:

1. The annual mortality of new cases varied so much from year to year as to make conclusions with regard to the value of treatment, as it affected the hospital mortality of diabetes during any one year, of but little value.

2. Diabetes became less severe as the age at which symptoms were first recognized became greater, although increasing years did not necessarily preclude a severe form of the disease.

3. There were four common causes of death. These were: (a) Coma with or without a terminal infection; (b) sepsis; (c) cardiovascular renal disease, including gangrene; (d) pulmonary tuberculosis.

Coma and pulmonary tuberculosis tended to occur more frequently in the younger patients; cardiovascular renal disease, including gangrene, in the older ones, and sepsis in those of any age.

The present paper is written by way of contrast to the earlier one, in an effort to determine whether any radical change in the clinical manifestations of diabetes has become apparent during the last decade since the introduction of this new therapeutic agent.

*The Hospital Mortality of Diabetes.* The diagnosis of diabetes mellitus was made in 562 cases admitted for the first time from the opening of the hospital, in 1913, until the end of 1922, and of these, 49 died in the hospital. From the beginning of 1923 to the close of 1933, 917 cases were admitted for the first time, and of these 66 died in the hospital. Thus the mortality rate of diabetes among new cases has remained nearly constant in spite of insulin, decreasing only from 9% during the pre-insulin period to 7% in the period during which insulin has been in use.

Study of the present series of cases confirms the conclusion of Fitz and Murphy in regard to the inconstancy of the hospital mortality of diabetes from year to year. In order to make this clear, the number of new cases admitted each year has been tabulated, and the number of deaths occurring among them (Table 1).

TABLE 1.—THE VARIABILITY OF DIABETIC MORTALITY.

Year.	New cases admitted.	New cases dying in hospital.	Mortality per 100 cases.
1923 . . . . .	133	11	8
1924 . . . . .	103	7	7
1925 . . . . .	91	2	2
1926 . . . . .	84	8	10
1927 . . . . .	97	4	4
1928 . . . . .	74	6	8
1929 . . . . .	69	8	11
1930 . . . . .	81	10	12
1931 . . . . .	59	6	10
1932 . . . . .	58	1	1
1933 . . . . .	68	3	4
Total . . . . .	917	66	—
Average . . . . .	83	6	7

The annual mortality for the new cases in the last 11 years has varied between 1% and 12%, with an average annual mortality of 7%. In the previous decade Fitz and Murphy noted a variation between 2% and 12% in the mortality rate during the different years, but with an annual average of 9%. They explained such variability by the fact that diabetes may be either a very mild or a severe type of disease. Any form of hospital treatment will appear to be accompanied by a low immediate mortality, if a sufficient number of mild cases is treated. On the other hand, a small series of severe cases will exaggerate the inevitable mortality which accompanies any chronic disease requiring hospital care. With as few cases as here reported, the sampling necessarily will be inadequate and fail to level out annual variations. This would be true of any disease with varying severity in individual cases.

*The Duration of Diabetes in Fatal Cases.* Of the 66 fatal cases in the present series, 48 were able to date the onset of their disease with a fair degree of accuracy. Thus the duration of diabetes was estimated and the results were arranged according to the age at the time of death (Table 2):

TABLE 2.—THE DURATION OF DIABETES.

Age at death.	Total number of cases.	Total duration of diabetic life, yrs.	Average duration of diabetic life, yrs.	Shortest duration of diabetic life, yrs.	Longest duration of diabetic life, yrs.
61 to 80 . . . . .	17	97.6	5.7	0.3	20
51 to 60 . . . . .	20	118.0	5.9	0.3	30
41 to 50 . . . . .	4	14.6	3.6	0.6	8
21 to 40 . . . . .	6	16.0	2.7	1.0	6
Less than 21 . . . . .	1	1.0	1.0	1.0	1
Total series . . . . .	48	247.2	5.1		
Series, Fitz and Murphy	55	225.0	4.1		

This table illustrates the well-known fact that diabetes tends to become less severe as the age at which symptoms are first recognized becomes greater. On the other hand, it also illustrates the fact that acute diabetes now as formerly may develop in persons of almost any age, so that increasing years do not necessarily preclude a severe form of the disease. The situation as here reported, however, differs in two important respects from that of 11 years ago. The most striking feature to be observed in a comparison of the two groups of cases is that fatalities in the younger age group now appear to be much less frequently met with than formerly. The previous study showed 21 deaths in persons below their 40th year, whereas the present study shows but 7 or, in terms of percentage, 38% of the deaths in the earlier series occurred in patients below 40, while but 14% of the younger cases in the present series have been fatal. This without doubt is due to insulin.

A second point which seems worthy of mention is that in the age group from 61 to 80 the average duration of diabetic life was 8.1 years in the earlier series and is 5.7 years in the present study. The apparent increase in the severity of diabetes in old people is of considerable interest. Perhaps the figures are misleading and are explainable, in part at least, by the fact that an unusual number of elderly patients in the present series entered the hospital with complications by necessity having a high mortality rate. For example, in the present elderly group there were 5 cases with coronary occlusions, 2 with cancer, 2 with general sepsis and 1 with a ruptured aneurysm. All of these complications might reasonably have proved fatal even if diabetes mellitus had not been present. It is significant, however, that of all the persons in the old age



group but 42% had ever received insulin prior to the hospital admission in which they died. One should not forget that the best modern treatment of even mild diabetes consists in the use of an appropriate diet on which the patients may remain sugar-free and in the proper use of insulin. The experience of this hospital suggests that insulin should be used more frequently in the management of elderly diabetics than formerly and that such cases deserve very careful supervision.

*The Cause of Death in Diabetes Mellitus.* Let us turn to the actual causes of death from which diabetic patients now are likely to succumb. Of the 86 diabetic patients who died in this hospital during the last 11 years, the true cause of death was ascertained by necropsy in 43. There were 2 cases of coma which showed no gross anatomic changes and in which the patients appeared to die from what might be called uncomplicated diabetic coma. There were 12 cases which, with or without coma, had an obvious sepsis or terminating acute infection. There were 3 cases of active pulmonary tuberculosis. There were 5 cases with unusual complications, such as acute nephritis (1 case) and carcinoma (4 cases). There were 21 cases with cardiovascular disease, including gangrene and chronic nephritis. The striking differences between the situation as it is at present and the situation 11 years ago, as reported by Fitz and Murphy, is best shown in tabular form with the figures reduced to a percentage basis:

TABLE 3.—THE CAUSES OF DEATH IN DIABETES MELLITUS AS PROVED BY NECROPSY.

	1913-1922, % of deaths.	1923-1933, % of deaths.
Coma . . . . .	11	5
Sepsis . . . . .	38	28
Cardiovascular disease . . . . .	24	49
Pulmonary tuberculosis . . . . .	19	7
Unusual complications . . . . .	8	11

At a glance two striking differences are to be seen between the fate of the pre-insulin diabetic and the diabetic of today. Deaths from coma, sepsis and pulmonary tuberculosis have shown a marked decrease, whereas those due to cardiovascular disease and its sequelæ have shown a marked tendency to rise. Coma, sepsis and tuberculosis accounted for about 70% of the deaths in the pre-insulin diabetics; they account for less than 40% of the diabetic deaths today. On the other hand, cardiovascular disease and its complications have increased in incidence to such a degree that they now account for approximately half of all diabetic deaths, whereas they formerly accounted for but 24%.

It would seem fair to credit the decrease in the incidence of coma and sepsis to the use of insulin. Physiologic studies have shown that insulin brings about complete oxidation of bodies of the ketone group, and these substances are considered to be the chief cause of

diabetic acidosis. By virtue of insulin one may rightfully expect uncomplicated coma to disappear from hospital records as a cause of death in diabetes save in those rare cases where the patient enters the hospital in the moribund state.

The decrease in sepsis may be explained by contrasting the nutritional condition of the diabetic today with that of the diabetic of a dozen years ago. At that time submaintenance diets were required in the treatment of practically all cases of diabetes. As a result of this procedure loss of weight was likely to occur. Today we may stabilize the patient's weight at the optimum by the exhibition of a suitable diet and the proper dose of insulin. In normal people resistance to infection is certainly enhanced by the possession of a body weight in the region of or just above the optimum. There seems to be no reason why similar reasoning should not hold in the case of diabetics.

The decrease in the incidence of tuberculosis as a cause of death in diabetes which was found in this clinic is not substantiated by the exhaustive studies of Root.<sup>2</sup> In a study of 2650 fatal cases of diabetes he found that pulmonary tuberculosis had increased from 4.7% of 342 deaths prior to June, 1919, to 6.7% of 1503 deaths between August, 1922, and November, 1931. The reasons for this increase are still matters of conjecture.

Cardiovascular disease, including gangrene and chronic nephritis, accounted for 24% in the present series. The great increase in deaths arising from this source suggests that the present mode of treatment has no effect whatsoever upon the development of vascular disease in diabetic patients. Many hypotheses may be invoked in order to explain this. One may say that insulin has such a pronounced effect upon coma and sepsis that a large number of diabetic patients live long enough to arrive at the age where vascular disease usually becomes manifest in non-diabetics. The fact that juvenile diabetics are subject to precocious vascular changes would seem to suggest that the arteriosclerotic process seen in these patients is a manifestation of the diabetes itself, rather than part of a separate aging process. Furthermore, the process seems to take place regardless of the exhibition of insulin. Future improvement in therapy should be directed toward this phase of the disease.

**Comment.** In contrasting the diabetic of today with the diabetic of a dozen years ago, one is gratified at the changes which have taken place. At the time when insulin was first discovered perhaps too much was expected as a result of its discovery. In envisaging its benefits, it was not realized that insulin would unmask a serious defect in diabetic therapy. The marked increase in the mortality arising from cardiovascular complications is probably the most outstanding defect in our present form of treatment. Our knowledge of these cardiovascular complications is by no means complete

at the present time. We know the pathology of these vascular changes, we know that they originate relatively early in the course of the disease, but we do not know their precise cause, and at the present time we know of no method by which we may cure them or prevent their occurrence.

Success in the management of any chronic and incurable disease is measurable:

1. By the prolongation of life.

2. By decreasing the disability due to the disease, and thus making life more endurable for the ones afflicted.

Judged by these criteria the modern forms of diabetic therapy has brought about the following improvements:

1. The average duration of life following the onset of the disease has been prolonged from 4.1 to 5.1 years.

2. The nutritional level of these patients has been raised, so that they no longer need to live in a state of constant discomfort and weakness due to semistarvation.

3. Coma is relatively infrequent, and if it does ensue, the newer mode of treatment will probably overcome it.

4. Sepsis is less frequent than formerly, and when it does supervene, our present method of treatment shows a great improvement over that which was formerly employed.

**Conclusions.** A study was made of the fatal cases of diabetes mellitus which were observed in this clinic from 1923 to the end of 1933. This was contrasted with the work of Fitz and Murphy, who reported the fatal cases observed here prior to the beginning of 1923.

The present study would appear to justify the following conclusions:

1. In both series of cases there were four common causes of death. These causes are coma, sepsis, pulmonary tuberculosis and cardiovascular disease, including gangrene and chronic nephritis.

2. Since the introduction of insulin, coma and sepsis have decreased in frequency; cardiovascular disease has shown an increase in frequency; unusual complications have remained practically unchanged.

3. The mortality rate of new cases of diabetes in this clinic has decreased from 9% prior to the introduction of insulin to 7% during the period of insulin therapy.

4. The present tendency is for coma and sepsis to be eradicated as a cause of diabetic mortality.

5. Our present mode of treatment appears to have no effect upon the form of cardiovascular disease which is seen in diabetic patients.

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## STUDIES IN DIABETES MELLITUS.

### III. INTERPRETATION OF THE VARIATIONS IN DIABETES INCIDENCE.

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IN two preceding papers<sup>1,2</sup> we have reviewed the increasing incidence of diabetes and its variations according to sex, locality, socioeconomic position and other groupings. These variations appear to reflect the interaction of two basic types of forces: constitutional or intrinsic, and environmental or extrinsic. This is evident both from the changing incidence of the disease in the same population over a period of time and in the differences exhibited by various population groups at a given time. Superficially, there would seem to be a distinction between these two types of variations. Actually, however, they are almost identical; for the changes in environmental conditions which favor a high incidence of diabetes are of such a nature as to affect an increasing portion of the population. For the most part, these variations represent real differences in the incidence of the disease but, to a certain extent, they are only apparent in that they represent differences in the known, in contrast to the actual, incidence. The purpose of this paper is to demonstrate the operation of the forces which cause the observed variations, and to distinguish the forces which produce real variations from those which produce apparent variations in the disease.

The data pertinent to the authors' viewpoint are not altogether satisfactory. They are either incomplete or unavailable, and often only indirect or inferential evidence can be offered. Indeed, assembly of fundamental data on certain of the subjects discussed in this paper is urgently needed. It is to be hoped that our admittedly incomplete discussion will stimulate research which will help to clarify those parts which are based on presumptive evidence. Until this is done, it is impossible to prove the authors' viewpoint by rigorous scientific methods. For this reason, largely, the authors have not used the method of correlation analysis to measure the

association between these factors in the changing incidence of the disease. Furthermore, the various factors are often not measurable either in their direct or indirect effects, or the weight of any single factor is so thinly and widely diffused that such methods of computation lead to erroneous or indefinite results.

*Constitutional Factors.* The chief constitutional feature in the onset of diabetes is overweight. This is clear whether we analyze the weights of known diabetics or take a group of supposedly non-diabetic persons and ascertain the subsequent history of various groups of them according to their weight.

TABLE 1.—MAXIMUM WEIGHT PRIOR TO ONSET OF DIABETES AND WEIGHT AT ONSET OF ADULT DIABETIC PATIENTS (AGES 20 AND OVER).

Percentage in Groups Classified by Deviation from Average Weight for Height and Age. By Sex. Experience of Elliott P. Joslin, M.D., 1898-1928.

Weight group.	Per cent.			
	Previous maximum weight.		At onset.	
	Males.	Females.	Males.	Females.
All cases . . . . .	100.0	100.0	100.0	100.0
Overweight, total: (5% or more above average) . . . . .	78.5	83.3	62.7	67.4
20% or more . . . . .	51.0	59.3	33.8	41.1
40% or more . . . . .	16.5	25.8	8.6	15.4
30% to 39% . . . . .	13.9	14.2	9.5	11.2
20% to 29% . . . . .	20.6	19.3	15.7	14.5
5% to 19% . . . . .	27.5	24.0	28.9	26.3
Normal weight (less than 5% above or below average) . . . . .	13.6	10.4	17.9	13.6
Underweight, total: (5% or more below average) . . . . .	7.9	6.3	19.4	19.0
5% to 19% . . . . .	7.1	5.5	16.3	14.9
20% or more . . . . .	0.8	0.8	3.1	4.1
Number of cases . . . . .	2251	2345	1613	1481

Clinical records show the great frequency of overweight among diabetics. The experience of Joslin (Table 1) is typical. The weight history of all adult diabetic patients, seen from 1898 to 1928, has been analyzed from two points of view: (1) The maximum weight prior to onset of the disease, and (2) weight at onset. Among 4596 patients for whom facts were available, 78.5% of the males and 83.3% of the females were overweight (5% or more above

average for age) at the time of their maximum weight. The weight of onset gave somewhat lower figures. Of the 3094 cases for whom these facts were noted, 62.7% of the males and 67.4% of the females were overweight. Moreover, one-half of the men and close to 60% of the women were at least 20% overweight at their maximum weight. Large numbers were extremely fat. No less than 16.5% of the men and 25.8% of the women were 40% or more overweight, at their maximum. In contrast with these high figures, only 7.9% of the men and 6.3% of the women had always been underweight (5% or more less than average for age) and less than 1% of the whole group had always been 20% or more underweight.

The importance of obesity in diabetes is also confirmed by insurance records, which show that its subsequent development among persons accepted for insurance after medical examination and known not to be diabetic is far more frequent among overweights than among persons of average weight or less. Thus, in the Medico-Actuarial Investigation,<sup>3</sup> covering the combined mortality experience of 43 insurance companies, between 1885 and 1909, on men insured at standard premium rates, 3 broad weight groups were distinguished, namely, 50 pounds or more overweight, 25 pounds or more underweight and "standard" weight, falling between these two extremes. Among those insured at ages under 30, the subsequent diabetes death rate of overweights was 15 per 100,000, compared to 6 among "standard" weights and 7 among underweights. Among those between 30 and 45 years when insured, the diabetes mortality was 59 per 100,000 for the overweights, 12 for "standard" weights and 5 for underweights. For those 45 years or over when insured, the diabetes death rate among overweights was 136, compared with 28 for the "standard" group and 6 for underweights. In this study, therefore, a large disparity existed between the diabetes death rates of overweights and persons of average weight or less, and this disparity increased with advancing age. In the recent Medical Impairment Study,<sup>4</sup> an investigation of the same type as the earlier one but covering the experience of 39 companies between 1909 and 1928, similar results were obtained. The findings of these two studies regarding diabetes and weight are summarized in Table 2.

Furthermore, the toll of diabetes increases with the degree of overweight. A study of the experience of the Union Central Life Insurance Company<sup>5</sup> showed that men who were 5 to 14% above average weight had a diabetes mortality only  $1\frac{1}{2}$  times that of normal weights, compared with  $3\frac{1}{2}$  times for those 15 to 24% overweight, and  $8\frac{1}{3}$  times for those 25% or more overweight. These differences were even larger at the ages of 45 and over; those 5 to 14% overweight suffered a mortality nearly twice that of normal weights, and those 15 to 24% overweight, nearly 4 times, while

those 25% or more overweight had a mortality over 10 times that of average weight men.

TABLE 2.—INFLUENCE OF WEIGHT ON MORTALITY FROM DIABETES. DEATH RATES PER 100,000 AMONG MALES ACCEPTED FOR LIFE INSURANCE AT STANDARD RATES. BY WEIGHT AND AGE GROUPS AT ISSUE.

	Supplement to medical impairment study, 1909-1928.			Medico-actuarial mortality investigation, 1885-1909.		
	Ages at issue:			Ages at issue:		
	10 to 29.	30 to 44.	45 and over.	15 to 29.	30 to 44.	45 and over.
Overweight (50 pounds or more above average)	15	19	35	15	59	136
"Standard" (less than 50 pounds above or 25 below average)	4	8	25	6	12	28
Underweight (25 pounds or more below average)	3	3	18	7	5	6

All fat people do not, of course, get diabetes. For example, in the Medico-Actuarial Investigation,<sup>3</sup> only 5% of the deaths of men 50 pounds or more overweight when insured, were due to diabetes. Other factors must be involved in the causation of the disease. Many have been advanced, such as heredity, infections, arteriosclerosis and pluriglandular disturbances. The most significant is probably heredity.\* Indeed, the factors of obesity and heredity are probably closely linked. Obese persons who become diabetic appear, for the most part, to be those with an inherited susceptibility to the disease, the obesity acting as the exciting factor to produce the disease. The importance of heredity is brought out by many careful analyses of family histories of diabetic patients, notably the studies of Pincus, White and Joslin<sup>6,7</sup> on Joslin's patients. It is also indicated by Tyner's<sup>8</sup> study of the weights of 500 patients with normal carbohydrate tolerance and 500 with impaired tolerance, but not frankly diabetic. Tyner found that "pre-diabetes" was more common in obese persons than among persons of normal weight only where there was a family history of diabetes.

The authors recognize that the relationship between obesity and diabetes is as yet not clearly defined. Diabetes has not been produced by overfeeding alone, experimentally or otherwise. The nearest approach to this has been the work of Allen,<sup>9</sup> who produced symptoms of the disease by fattening partially depancreatized dogs. It is possible, and even likely, that the connection between

\* Variations in diabetes incidence may, in part, be due to differences between populations in the distribution of the gene involved in the production of diabetes. It is not yet possible to estimate for any population how widely distributed this gene is.

obesity and diabetes is not a causal one and that both reflect some underlying imbalance in the functioning of the body, probably of endocrine origin. Despite this, however, the association of diabetes with a preceding obesity is so close that conditions favoring obesity are undoubtedly related to concomitant variations in the incidence of diabetes. Overweight as the exciting factor of the disease in susceptible individuals so much overshadows the other factors that the present discussion is largely devoted to it and the conditions favoring it.

Certain faults in the definition of obesity should also be noted. The usual standards, based upon arbitrary percentages above average weight, are, at best, approximations. Indeed, they lead to definite understatement of the degree and incidence of overweight. For, a characteristic of these standard tables is the increase of weight with age, a development which is neither inevitable nor physiologically sound. From the standpoint of mortality, the best weights—those which give the lowest mortality in adult life—are appreciably below the average.<sup>10,11</sup> They tend to correspond to the average weights of the late twenties or early thirties. If mortality is the best guide to what constitutes normal weight, our current standards are all too liberal. Another and possibly more fundamental objection is that these average weights leave out of consideration differences in bodily proportions, and the relative weights of the skeletal structure, muscle and fat. It may very well be that entirely different measures of obesity are needed. Suggestive in relation both to obesity and diabetes is the fact that the proportion of fatty tissue to total body weight is normally greater in women than in men throughout adult life. Significant differences also exist between persons of the same general build, but differing in musculature.

*Environmental Factors and Their Relationship to Constitutional Factors.* Most overweight results from overnutrition.<sup>12</sup> Even if, as previously suggested, a glandular disturbance is sometimes involved in obesity, it does not operate in the absence of overfeeding, absolute or relative. Whatever increases the chances of becoming overweight, therefore, will tend to bring about a real increase in the incidence of diabetes in susceptible overweights. Consequently, whenever and wherever conditions of life are easy, food abundant and relatively cheap over long periods, and when large numbers of individuals become accustomed to partake of food in excess of their requirements for the expenditure of energy, the frequent development of overweight and of diabetes is favored. These factors are also believed to underlie the differences in diabetes incidence in climatic areas demonstrated by Mills.<sup>13</sup>

Three broad groups of phenomena are involved in this theory, namely, mass variations in *per capita* energy requirements, food consumption and variations in the incidence of overweight. Data



only on the first of these are abundant and are presented in detail. In the case of the others, primary data are not available and we are forced to depend upon indirect evidence. For information on food consumption, we make use of certain indices, admittedly imperfect, such as income and purchasing power, because the facts on food consumption in the necessary detail do not exist. Moreover, because dietary habits have changed a great deal everywhere it is difficult even to determine whether food consumption on a caloric basis has really changed. In the United States it has apparently declined,<sup>14</sup> but not to a degree commensurate with the fall in *per capita* energy requirements. Facts on group variations in the frequency of overweight or on the increase in its incidence are also lacking. Because of the close association between diabetes and overweight, however, variations in the incidence of diabetes are presumed to correspond with variations in the incidence of obesity. For example, as we shall show in a later paper, Jewish diabetics are as frequently overweight as other patients. This indicates that the greater incidence of the disease in Jews must reflect a greater frequency of obesity. Probable evidence of increasing frequency of overweight is also indirect. It may only be inferred from insurance data on build, which show that there has been no decline in average weights among persons accepted for "Ordinary"\* insurance,<sup>15</sup> although this type of insurance has been extended in large volume since 1919 to the working classes, among whom overweight is presumably less frequent than in the better situated classes.

THE SIGNIFICANCE OF CONDITIONS FAVORING OVERWEIGHT.  
 (a) *Occupation and Social Status.* Our preceding paper<sup>2</sup> showed that rural death rates from diabetes are lower than urban rates. In rural communities, hard manual work is usual, particularly among farm laborers. The analysis of English occupational mortality, largely confirmed by recent American data,<sup>16</sup> showed that the incidence of diabetes among workers of this type was among the lowest recorded. Farmers and their families, however, who, on the average, do less work and are generally better fed and circumstanced, had a diabetes rate more than twice that of their laborers. In similar fashion, those engaged in coal mining, another type of work frequently involving hard manual labor and concentrated in rural districts, also had a very low mortality from diabetes. The high diabetes rates in cities, therefore, may be ascribed, in part, to the lighter work done by relatively large numbers of the urban population. Thus, our study of occupations showed high rates for persons engaged in professional callings and in clerical and mercantile pursuits, which usually require little actual labor. Yet, in these same urban areas, low rates are found among those doing hard manual work, for example, among laborers of all kinds.

\* Insurance written in amounts of \$1000 or more on an annual, semiannual, or quarterly basis.

Diabetes mortality of artisans, whose work usually requires a moderate amount of physical activity, is midway between that of the professional and laboring groups. Similarly, the differences in diabetes mortality between the various social classes, disclosed in our preceding paper reflect, to a great extent, merely the varying proportions of persons engaged in light and heavy work.

The high diabetes death rate among Jews may, in part, be due to the same causes. They have been for several generations an urban people. For a long time they were restricted to certain occupations and were not permitted to own land or till the soil. Relatively large numbers were engaged in the professions and in business. Despite the removal of earlier restrictions, succeeding generations have naturally followed the same sedentary occupations.

(b) *Regional Variations in Earnings.* As we have seen, the United States has the highest diabetes death rate in the world. Relatively high rates prevail in most of the British colonies. In Europe the rates in the northern countries are higher than those in the south and east, which means that they are higher among the Germanic groups than among the Latins and the Slavs. It is precisely in countries where diabetes is most frequent that the level of *per capita* income is high, and it is reasonable to assume that the level of nutrition corresponds with *per capita* income. The facts on comparative "real" earnings in the large cities (usually the capitals) of several countries, which are given in Table 3, are taken from the most careful study of the kind, made by the International Labour Office of the League of Nations.<sup>17</sup> International comparisons of this type are not altogether satisfactory because suitable standards are hard to devise, but the study quoted offers the most comparable data available.

It will be seen at once that the standards of living are reflected in the differences in diabetes mortality. Yet certain limitations of the data must be recognized. The groups considered were skilled and unskilled workmen in a few trades in which organization is often best and bargaining power highest. The proportion of unorganized semiskilled workmen and of industrial laborers was low. No consideration was given to agricultural laborers who, in many countries, constitute the largest group in the working population. The important mercantile and clerical groups were likewise excluded. To offset these deficiencies, however, it should be noted that the earnings of industrial, mercantile, clerical and agricultural groups stand roughly in the same relation to each other in all countries.

In the United States, also, regional variations in diabetes death rates tend to correspond with variations in income. Jordan,<sup>18</sup> taking the percentage of those filing income tax reports in the various states as an index of economic well-being, found that those states where the percentage was high usually had above average

rates from diabetes. *Per capita* realized income<sup>19</sup> in the several sections of this country also tends to correspond with the level of the diabetes death rates in the same areas. Table 4 shows that the diabetes rates are highest in the Middle Atlantic and New England states, where incomes are appreciably above the average, and lowest in the South, where the average income is low. The figures for the Mountain and Pacific regions are out of line. The income figures relate to the year 1919, but index figures for 1926, with 1919 taken as a base, show no material change in regional differences in income.<sup>20</sup>

TABLE 3.—STANDARD OF LIVING OF WORKERS IN VARIOUS COUNTRIES.

Number of Baskets of Provisions\* Purchaseable with Wages as of October 1, 1926, based on the Average Wage for a 48-hour Week in Certain Industries, as Fixed by Collective Agreement. Base: London = 100.

City.	Index numbers of purchasing power of wages.			
	Several industries combined.†		Machinery manufacture—expert mechanics and machinists (no adjustment for rent).	Printing industry—hand compositors (no adjustment for rent).
	No adjustment for rent.	With adjustment for rent.		
Philadelphia . . . . .	183	183	179 <sup>2</sup>	125 <sup>2</sup>
Ottawa . . . . .	159	157	191	153
Sydney . . . . .	137	137	163	109
Copenhagen . . . . .	125	125	142 <sup>1</sup>	97 <sup>1</sup>
London . . . . .	100	100	100	100
Amsterdam . . . . .	96	96	112	84
Stockholm . . . . .	92	90	..	73
Oslo . . . . .	80	82	112 <sup>2</sup>	90 <sup>2</sup>
Berlin . . . . .	69	63	84 <sup>4</sup>	56
Paris . . . . .	60 <sup>2</sup>	61 <sup>2</sup>	60	48
Madrid . . . . .	56 <sup>3</sup>	..	70 <sup>2</sup>	56 <sup>2</sup>
Warsaw‡ . . . . .	55	56	45	87
Prague . . . . .	50	53	62	..
Rome§ . . . . .	46	48	55	40
Vienna . . . . .	44	50	51	40
Brussels . . . . .	44	47	59 <sup>2</sup>	52 <sup>2</sup>

\* Separate indices were prepared based upon a series of typical food budgets for each of the following countries or groups of countries: Belgium and France, central European countries, Great Britain, southern European countries, Scandinavian countries, United States and British colonies. The figures presented are the averages of these separate indices.

† (a) Building trades: masons and laborers; (b) machinery manufacture: expert machinists and mechanics and laborers; (c) furniture manufacture: cabinet makers and laborers; (d) printing and bookbinding: hand and machine compositors and laborers.

‡ Wages are far higher than in other towns of Poland, particularly for the groups of workers studied.

§ Figures are relatively low because comparisons do not make adequate allowance for the high vegetable consumption in southern European countries.

<sup>1</sup> January 1, 1926; <sup>2</sup> April 1, 1926; <sup>3</sup> July 1, 1926; <sup>4</sup> October 1, 1924.

TABLE 4.—REGIONAL VARIATIONS IN INCOME AND DIABETES MORTALITY PER 100,000 IN THE UNITED STATES.

Per Capita Realized Income, 1919; Index of Income in 1926 (1919 = 100) and Standardized Death Rates from Diabetes, 1929-1931, Nine Census Regions.

Region.	Income.		Diabetes death rates.
	Per capita, 1919.	1926 index (1919 = 100).	
United States . . . . .	\$614	...	17.1
New England . . . . .	715	114	17.9
Middle Atlantic . . . . .	781	133	22.3
East North Central . . . . .	669	121	17.8
West North Central . . . . .	582	93	16.3*
South Atlantic . . . . .	445	106	14.1
East South Central . . . . .	345	107	11.4
West South Central . . . . .	469	95	10.8†
Mountain . . . . .	634	92	13.0
Pacific . . . . .	793	120	14.2

\* Excludes South Dakota.

† Excludes Texas.

TABLE 5.—REGIONAL VARIATIONS IN EARNINGS OF FACTORY WORKERS AND COMMON LABORERS AND DIABETES DEATH RATES IN THE UNITED STATES.

Estimated Annual Full Time and Actual Earnings of Factory Workers in 1923; Hourly Wage Rates of Common Laborers, January 1, 1928; and Total and Urban Diabetes Death Rates Per 100,000, 1928-1929.

Region	Factory workers, annual earnings.		Common laborers, hourly wage rates.	Diabetes death rates.	
	Full-time.	Estimated actual.		Total.	Urban.
United States . . . . .	\$1,545	\$1,317	\$0.43	18.9	24.4
New England . . . . .	1,396	1,181	0.47	23.8	24.8
Middle Atlantic . . . . .	1,774	1,501	0.49	24.5	27.4
East North Central . . . . .	1,798	1,521	0.47	21.4	23.2
West North Central . . . . .	1,511	1,278	0.41	20.1*	25.4*
South Atlantic . . . . .	1,091	962	0.29	12.7	21.2
East South Central . . . . .	1,111	980	0.27	10.6	21.1
West South Central . . . . .	1,152	1,016	0.31	9.6†	19.2†
Mountain . . . . .	1,661	1,556	0.44	13.8	21.6
Pacific . . . . .	1,717	1,609	0.47	18.4	21.6

\* Excludes South Dakota.

† Excludes Texas.

Similar regional relationships exist between the incomes of wage workers and diabetes rates. Table 5, which gives data on earnings of factory workers<sup>21</sup> and common laborers<sup>22</sup> in the 9 census areas, shows practically the same order as the preceding table. The averages given for factory workers relate to hypothetical full-time and actual earnings in 1923. The figures for the Mountain and

Pacific Coast states are much out of line with the diabetes death rates also shown in the table; but in both these areas, relatively few persons are engaged in factory work, and, moreover, in the Mountain states the average age of the population is low. The hourly wage rates of common laborers, as of January 1, 1928, show the same regional characteristics as factory wages, namely, relatively high rates in the Northeast and Pacific Coast states, average rates in the Middle West and low rates in the South. These regional death rates are crude rates. Consequently no allowance is made for differences in the proportion of older persons in the several regions. Unfortunately, necessary data are lacking to correct for this factor both in this and succeeding comparisons.

In agricultural regions, also, general agreement between diabetes incidence and income is found in the several parts of the United States. For this comparison, we are limited to rather old material, namely, Leven's estimate of *per capita* farm earnings in 1919-1921<sup>23</sup> (Table 6). Estimates of *per capita* income and income per farm family are given and, for comparison, diabetes death rates for rural areas are included. Again, high *per capita* income and high diabetes death rates appear to go together. To complete the picture, the earnings of agricultural laborers<sup>24</sup> (Table 6) also vary in the same way as the diabetes rates. These facts relate to prevailing rates of farm wages as of October 1, 1930. Later data are available, but are not used because the figures are abnormally low, although regional relationships are maintained.

TABLE 6.—REGIONAL VARIATIONS IN PER CAPITA FARM INCOME AND WAGE RATES AND IN RURAL DIABETES DEATH RATES IN THE UNITED STATES.

Per Capita Current Income (Excluding Value of Rent) of Farm Population and Income Per Farmer and Family, 1919-1921; Monthly and Daily Wage Rates for Farm Laborers, October 1, 1930, and Rural Death Rates Per 100,000 from Diabetes, 1928-1929.

Geographic division.	Income.		Wage rates.*		Rural diabetes death rates.
	Per capita farm population.	Per farmer (and family).	Monthly.	Daily.	
Continental United States . . . . .	\$282	\$1,158	\$44.28	\$2.12	14.3
New England . . . . .	437	1,355	64.65	3.27	{ 21.5
Middle Atlantic . . . . .	473	1,626			{ 19.2
East North Central . . . . .	337	1,289	50.14	2.60	{ 19.3
West North Central . . . . .	296	1,074			{ 17.6†
South Atlantic . . . . .	195	987	31.65	1.46	9.6
East South Central . . . . .	159	740	31.23	1.40	{ 8.2
West South Central . . . . .	242	1,104			{ 7.2†
Mountain . . . . .	446	1,653	73.97	3.14	{ 11.0
Pacific . . . . .	748	2,451			{ 14.7

\* Without Board. Wages with board vary in same proportions.

† Excludes South Dakota.

‡ Excludes Texas.

(c) *Extent of Industrialization and Urbanization.* The differences in the level of diabetes incidence in the various parts of the world, as well as within individual countries, also reflect the extent to which the inhabitants depend upon purely industrial, mercantile and professional pursuits, as opposed to farming and other activities requiring much physical labor. This phase of the problem is closely connected with the extent of urbanization, and it is impossible to disentangle the influence of each. Industrial and mercantile nations, which tend to be those having a large percentage of their populations in urban areas, usually show high *per capita* incomes and high diabetes rates. The factors of industrialization and high earnings really reinforce each other. Despite their lower *per capita* food requirements, workers in industrial and mercantile countries are able to buy as much food as those in countries where the greater

TABLE 7.—REGIONAL VARIATIONS IN OCCUPATION,\* IN THE PERCENTAGE OF THE POPULATION LIVING IN URBAN† AREAS, AND IN THE DIABETES DEATH RATE.

Country.	Per cent in specified occupation groups.			Per cent urban population.‡	Diabetes death rate per 100,000.§
	Agriculture and forestry.	Manufacturing and handicrafts.	Trade, transportation, communication and personal service.		
United States (1930)	22.0	28.9	30.5	56.2	19.4
New England . . .	6.8	43.1	30.2	77.3	24.4
Middle Atlantic . . .	5.4	36.3	34.0	77.7	25.5
East North Central . . .	14.7	35.7	30.7	66.4	21.4
West North Central . . .	33.8	19.9	29.9	41.8	20.6
South Atlantic . . .	33.4	24.2	27.6	36.1	13.5
East South Central . . .	48.3	16.9	23.1	28.1	11.0
West South Central . . .	41.1	16.9	28.3	36.4	9.7
Mountain . . .	31.7	18.3	29.1	39.4	13.3
Pacific . . .	16.3	26.1	35.8	67.5	18.6
Canada (1931) . . .	31.1	28.5	25.7	53.7	12.8
England (1921) . . .	6.8	39.7	32.7	80.3	15.2
Belgium (1920) . . .	19.1	39.9	23.3	60.5	15.9
Holland (1930) . . .	20.6	37.2	30.9	78.8	17.6
Norway (1930) . . .	35.3	25.9	32.1	28.5	11.6
Sweden (1920) . . .	40.7	30.2	21.3	32.5	13.8
Denmark (1921) . . .	34.8	27.0	30.0	43.9	17.9
Czechoslovakia (1930) . . .	28.3	40.4	19.3	47.8	9.3
Italy (1931) . . .	46.3	30.4	16.0	42.5	8.2
Australia (1921) . . .	22.9	31.2	33.3	63.8	15.3
New Zealand (1926) . . .	24.2	24.3	33.9	51.6	15.7

\* In most countries, persons engaged in clerical work are assigned to the branch of industry to which they are attached. In the United States they are tabulated separately. In 1930 they accounted for 8.2% of gainfully employed persons.

† The definition of urban population differs from place to place. Usually it includes the population of incorporated cities and towns with a limit of 2000 or upwards. In Czechoslovakia, figures relate to communes of 2000 or over; and in Belgium and Holland, to communes of 5000 and over.

‡ Calculated for the same years as the occupational data, except Australia, 1933; England, 1931; Belgium, Sweden and Denmark, 1930; Italy, 1921.

§ 1932, except Belgium and Sweden, 1931; Italy, 1930; United States, 1929-1931.

number of inhabitants depend upon more arduous occupations for their livelihood. Consequently, one should expect a greater frequency of overweight and, therefore, of diabetes, in industrialized and urbanized communities. These tendencies are indicated in Table 7, which shows national differences and, for the United States, regional differences in diabetes mortality, in the proportion of persons in agricultural and two broad non-agricultural groups,<sup>25,26</sup> and in the proportion of the population living in urban areas.<sup>27,28</sup> The reader is cautioned, however, that there are certain differences in the classification, both of occupational groups and of urban populations; and on that account the figures given are general rather than absolute guides.

*Evidences in Diabetes Trends of Conditions Favoring Overweight.* The same forces which make for real differences in diabetes mortality between various countries and between areas within them are largely responsible for the upward trend of diabetes incidence and mortality. Most important of these are mechanization and the rising standards of living, which have been responsible for many profound changes in the structure of the modern world. These two not unrelated forces have acted in quite different ways to increase the incidence of diabetes by disturbing the metabolic equilibrium of large numbers of persons.

TABLE 8.—OCCUPATIONAL SHIFTS IN THE UNITED STATES, 1870-1930.  
Per Cent of Gainfully Occupied Persons in Certain Broad Occupational Groups  
and in Certain Specific Occupations.

Occupation group.	1870.	1900.	1930.
Total	100.0	100.0	100.0
Agriculture and allied occupations	52.8	35.9	21.3
Mining	1.5	2.1	2.0
Manufacturing and mechanical industries	22.0	27.5	28.6
Trade and transportation	9.1	16.3	20.7
Total trade	..	9.6*	12.7
Sales people and clerks in stores	0.9†	3.0†	4.9
Clerical service	1.7	2.8	8.2
Domestic and personal service	9.6	10.0	11.3
Launderers, outside home	..	0.4*	0.5
Barbers and manicurists	0.2	0.5	0.8
Public service not elsewhere classified	0.6	1.0	1.4
Professional service	2.7	4.4	6.5

\* 1910.

† Estimated.

(a) *Occupational Changes.* The first important result of mechanization has been a flow of workers from more arduous occupations into jobs requiring less expenditure of energy. For the United States this is clearly brought out in Table 8, which shows the per cent distribution in 1870, 1900 and 1930 of gainfully occupied persons, 16 years of age and over, in certain broad occupational classi-

fications and for a few specific types of work.<sup>29</sup> In the interval of 60 years, between 1870 and 1930, the number of persons engaged in agricultural and allied occupations dropped from 52.8 to 21.3% of all occupied persons. Large absolute gains have been made in

TABLE 9.—CHANGES IN PROPORTIONS OF WORKERS ENGAGED IN AGRICULTURE, INDUSTRY AND TRADE IN SEVERAL COUNTRIES.

	Per cent.		
	Agriculture.	Manufacturing and mechanical trades.	Trade.
Australia:			
1921 . . . . .	22.9	31.2	15.3
1911 . . . . .	24.2	28.4	14.5
1901 . . . . .	†	26.1	13.6
Canada:*			
1931 . . . . .	31.2	...	12.2
1921 . . . . .	35.0	26.5	11.8
1901 . . . . .	42.6	28.0	9.0
England and Wales:*			
1921 . . . . .	6.8	39.7	13.9
1911 . . . . .	7.7	38.7	13.4
Great Britain:			
1911 . . . . .	8.5	18.4‡	...
1901 . . . . .	8.9	17.8‡	...
Belgium:			
1920 . . . . .	19.1	39.9	10.7
1910 . . . . .	22.5	40.4	11.9
Denmark:			
1921 . . . . .	34.8	27.0	10.8
1911 . . . . .	41.7	24.2	10.4
France:*			
1926 . . . . .	38.3	31.2	11.5
1921 . . . . .	41.5	28.4	10.4
1906 . . . . .	42.7	28.8	9.7
Germany:			
1925 . . . . .	30.5	41.4	16.5
1907 . . . . .	34.0	39.1	13.9
1895 . . . . .	36.4	37.7	10.9
Netherlands:			
1930 . . . . .	20.6	37.2	14.0
1920 . . . . .	23.6	36.1	11.7
1909 . . . . .	28.4	34.2	10.8
Norway:			
1930 . . . . .	35.3	26.5	12.5
1920 . . . . .	36.8	27.4	11.1
1910 . . . . .	39.5	25.1	8.8
Sweden:*			
1920 . . . . .	40.7	30.2	8.4
1910 . . . . .	46.3	25.1	5.4
Switzerland:			
1930 . . . . .	21.3	44.6	14.6
1920 . . . . .	26.6	44.7	11.7
1900 . . . . .	32.2	46.1	9.3

\* Includes all persons connected with each branch of industry. In all other cases the classification is according to occupation.

† Primary producers (farmers and their laborers, cattlemen, miners, etc.) 1900, 32.5%; 1911, 30.4%; 1921, 25.8%.

‡ Selected manufactures.



the percentage employed in factories, but by far the greatest gains, absolutely and relatively, are recorded for trade and transportation, clerical work, professional and semiprofessional occupations and public employment. In the trade and transportation groups, much the largest gain has been made by the trade group. The number of persons engaged in domestic and personal service, as a whole, has shown a very slight upward trend, but the increase seems to be concentrated in personal service, especially among such workers as waiters and other restaurant employees, barbers, hairdressers, manicurists and launderers working outside the home.

Similar occupational changes are noted in most other countries.<sup>25</sup> Since the World War, these changes have been accelerated by the policies of economic nationalism, especially in the European countries set up after the conflict. The extent of this is not fully demonstrable because of the lack of sufficiently detailed or up-to-date statistics and because of boundary changes. Despite these difficulties, the world-wide trend from agricultural to manufacturing pursuits, clerical and professional work and certain types of personal service is evident in Table 9.

(b) *Increased Use of Power.* Coincident with this change in the occupational pattern, there has been a drastic reduction in the amount of human labor through the use of power-driven machinery. The extent of the change in the United States is shown by comparing the changes in the number of wage earners engaged in manufacturing and in the rated horsepower capacity of plant equipment.<sup>30</sup> The increase in power-driven equipment has far outstripped that in the number of wage earners. In the 30-year period, 1899 to 1929, the number of wage earners increased only 88%, compared with an increase of 331% in power equipment capacity. In the decade between 1919 and 1929, despite a slight decrease in the number of wage earners, the power capacity increased nearly 50%. The horsepower per worker rose from 2.1 in 1899 to 3.3 in 1919 and 4.9 in 1929.

This development is not limited to the manufacturing industries alone. There has likewise been a rapid expansion of the use of machines driven by mechanical power in other types of work, in mining, in officework, on the farm and even in the home. Exemplifying the change in the farm picture is the enormous growth in the use of tractors in this country from only 80,000 in 1918 to 447,000 in 1923 and 853,000 in 1929, the last year for which the figures are available.<sup>31</sup> Thus, in the short period of 11 years the number of tractors in use increased over  $10\frac{1}{2}$  times, while the number of farmers and their laborers changed little.

The increase in labor-saving devices in the home is indicated by the rapid increase in the domestic consumption of electricity.<sup>32,33</sup> In 1913, the first year for which figures are available on a national scale, the domestic consumption of electricity was 1,025 million

kw. hrs. By 1923, the consumption had increased to 4,300 millions; in the succeeding 9 years, to 11,987 millions. In the 19 years, between 1913 and 1932, domestic consumption of electricity increased elevenfold, while the population rose about 30%. Much of this increase in domestic electrical consumption is, of course, accounted for by home lighting, but no small part of it is attributable to use of domestic labor-saving devices, which have increased steadily in recent years.<sup>34</sup> In connection with the reduction in domestic labor, mention should be made of the increased use of gas and electricity for cooking purposes in place of the old-fashioned coal stove, and also of oil and gas for domestic heating in place of coal furnaces.

The replacement of human labor by power-driven machinery is a characteristic development of our times. It is found in every country. Its extent varies from place to place, although it is difficult, if not impossible, to measure these differences. A sufficient indication is the increase in the output of electrical power in several countries between 1925 and 1931 (Table 10).<sup>35</sup>

TABLE 10.—INCREASE IN OUTPUT OF ELECTRIC POWER IN PRINCIPAL COUNTRIES OF THE WORLD, 1925 TO 1931.

Country.	Output of electric current* (millions of kilowatt-hours).	
	1925.	1931.
United States . . . . .	73,791	91,700
Canada . . . . .	10,480	16,383
Belgium . . . . .	3,214	3,851†
Denmark . . . . .	223	501‡
France . . . . .	9,700	13,974
Germany . . . . .	11,521	25,260
Italy . . . . .	7,600	10,603
Netherlands . . . . .	896	1,878
Norway . . . . .	4,200	10,500‡
Poland . . . . .	1,300	2,865§
Sweden . . . . .	3,500	4,982‡
Switzerland . . . . .	4,190	5,707†
United Kingdom . . . . .	8,320	11,401
Japan . . . . .	6,400	13,780§

\* In most cases figures cover central stations only, not isolated plants.

† Estimated.      ‡ 1929.      § 1930.

(c) *Increase in "Real" Incomes.* The development of modern machine industry has brought about a large increase in the productivity of the workers. In the United States,<sup>36</sup> if 1899 is taken as a base, the index for physical volume of production in 1929 was 310 for manufactures, 338 for transportation (railroad ton miles) and 386 for mining, whereas the index of population was only 162. Agriculture failed slightly to keep pace, its index of production reaching 148, but this is partly offset by a decline in the exportable

surplus. The result of this greater productivity has been an increase in the "real" incomes of the masses, both in this country and abroad. This has, of course, not been an uninterrupted development. The length and severity of the depression, which began in 1929, have in some quarters aroused the fear that there is to be an extended recession in living standards of the masses. It is probably a saner judgment, however, that this depression, like earlier ones, will prove no more than a temporary and cyclical one and that the upward trend in industrial production and the consequent improvement in living standards will be resumed. A definite increase in the "real" incomes over and above changes in price levels took place during the two decades preceding 1928. This is brought out clearly in Table 11, which gives Douglas' indices of real earnings of persons in all types of work and in the principal industrial groups<sup>37,38</sup> and Brissenden's indices of earnings for all factory workers.<sup>39</sup> To eliminate cyclical variations, 3-year averages are used. It will be noted that the increase in "real" incomes has not been concentrated in favored groups, but extends to every branch of activity. Although the increase varies from one industry to another, it is distinct in each of them.

TABLE 11.—TREND OF REAL EARNINGS IN THE UNITED STATES, 1899 TO 1928.

Index Numbers of Annual Earnings, Adjusted for Changes in Price Levels, of All Workers and Workers in Certain Manufacturing and Other Industries. (Estimates by Douglas except as noted.) 1914 = 100.

Period.	Manufacturing industries.											Clerical work.
	All workers.	All factory workers* (Brissenden).	All factory workers.	Food.	Textile.	Clothing.	Iron and steel.	Lumber.	Paper and printing.	Land vehicles.	Public utilities.	Coal mining.
1899-1901 . . .	93	104	100	101†	102	101	100	99	97	86	96	106
1904-1906 . . .	96	109	101	100‡	99	104	99	103	98	89	93	111
1909-1911 . . .	98	105	101	102	99	104	99	90	97	97	95	108
1914-1916 . . .	103	111	102	102	104	104	102	102	101	107	102	111
1919-1921 . . .	109	116	114	111	119	116	114	106	106	110	109	121
1924-1926 . . .	124	141	128	124	129	129	128	118	135	126	117	133
1928 . . .	132	140†	...	128	131	135	134	123	144	138	122	133

\* With allowance for unemployment and overtime.

† 1927.

‡ 1899.

§ 1901.

Similar changes in incomes and presumably in standards of living are noted in other countries as well. The most adequate study of this type was made by the International Labour Office of the League of Nations,<sup>40</sup> but unfortunately closes in 1925, when some countries had not yet recovered from the effects of post-war inflation of currencies or other financial or economic difficulties. Examination of Table 12, which gives a comparison of "real" wages in 1913-1914 and 1925 for workers in several countries reveals a distinct improve-

ment in workers' earnings in most of them. Countries in which there was little or no depreciation of currency have been segregated from the rest. In general, the improvement in incomes has been greater in them than in other countries. It is most significant, too, that in general the position of the poorer paid workers, the unskilled, has shown greater improvement than that of skilled workers. Prior to 1914, also, it is believed, "real" incomes of workers were improving in most countries.

TABLE 12.—REAL WAGES IN VARIOUS COUNTRIES IN 1925 COMPARED WITH PRE-WAR WAGES.

Index Numbers of Real Wages for Two Groups of Countries: Those With Little or No Post-war Depreciation of Currency (Group A) and Those With Large Depreciation of Currency (Group B). (1913-1914 = 100.)

Country.	Metal and engineering trades.		Building trades.		Printing trades.		Textile trades.		Mining.	
	Skilled.	Unskilled.	Skilled. (carpenters).	Unskilled.	Skilled (compositors).	Unskilled.	Skilled.	Unskilled.	Skilled.	Unskilled.
GROUP A:										
United States .	116 <sup>3*</sup>		113 <sup>6</sup>	116 <sup>6</sup>	120 <sup>3*</sup>		135 <sup>3,8*</sup>			
Canada <sup>1</sup> . . .	120 <sup>*</sup>		116		131 <sup>7</sup>				132	
Australia . . .	117 <sup>*</sup>		109 <sup>*</sup>		116 <sup>*</sup>				109 <sup>*</sup>	
New Zealand <sup>1</sup>	90		93	90			104			
Great Britain	84	102	105 <sup>6</sup>	119 <sup>6</sup>	120		118 <sup>8*</sup>		89 <sup>*</sup>	
Switzerland <sup>2</sup> .	127		120 <sup>6</sup>	121 <sup>6</sup>						
Netherlands . .					135 <sup>2</sup>		122 <sup>2</sup>		105	
Sweden . . . .	120 <sup>1*</sup>		125	139	130 <sup>1*</sup>		103 <sup>*</sup>			
Norway <sup>1</sup> . . .	111 <sup>*</sup>		95	97						
Denmark . . .	129	125	124	143	107	114	131			
GROUP B:										
France . . . .	109 <sup>1</sup>		123 <sup>1,6</sup>	126 <sup>1,6</sup>	126 <sup>1,4</sup>		131 <sup>1*</sup>		101 <sup>*</sup>	
Germany . . .	86	91	94	101	86	91	83	81	94	
Austria . . .	108	120	150	164	103 <sup>7</sup>		98			
Poland . . . .	69 <sup>1</sup>	83 <sup>1</sup>	89 <sup>4,6</sup>	144 <sup>4,6</sup>	181		66 <sup>5</sup>			
Czechoslovakia	87	81	86 <sup>4</sup>	87 <sup>4</sup>	99					

<sup>1</sup> 1924.      <sup>2</sup> 1923.      <sup>3</sup> New York.

<sup>5</sup> Lodz.      <sup>6</sup> Bricklayers.      <sup>7</sup> Total.

<sup>4</sup> Capital city.

<sup>8</sup> Average cotton and wool workers.

\* Skilled and unskilled combined.

To a certain extent the movement of "real" wages understates the improvement in living standards. In the first place, the size of workingmen's families has fallen as fast as in other sections of the population, and, consequently, there are, on the average, fewer persons to provide for with the wages earned. In the second place, average wages do not completely reveal the family income. The more frequent employment of women in industry, especially of married women, has increased family earnings to a far greater extent than the changes in *per capita* earnings would indicate.

There are, moreover, important additions to "real" income through the increased amount of free services supplied by the state or by private philanthropies. Certain factors, in part, offset these hidden additions to income, as, for example, the greater proportion of income which must be spent on rent in growing industrial areas.

(d) *Increased Leisure.* Another byproduct of our mechanized civilization is the increasing amount of leisure. Not only do men work less hard during their occupied hours, but they have more free hours. Fifty years ago, the 60-hour week was general in the United States, Germany, France and Belgium, a 52-hour week in England, but 72 hours in Italy, Russia and other countries. Even longer hours of work were not uncommon.<sup>41</sup> Since 1890, there has been a marked reduction in hours of labor. There are no comprehensive statistical data on the subject, but there is enough material to show the trend. In the United States, Douglas estimates the average working hours in certain trades at 58.4 in 1890, 57.3 in 1900 and 53.8 in 1913. A survey by the National Industrial Conference Board shows a decline for manufacturing industries from 55 hours in 1914 to 49.6 in 1927. Just before the World War, in many countries the 8-hour day already had obtained a strong foothold, especially in unionized industries. After the World War, the 8-hour day became even more general, expedited by international agreement. By 1928, a working week of 48 hours or less was enjoyed by more than 80% of full-time workers in England, Austria, Belgium, Czechoslovakia, Denmark, Holland and Sweden. In highly unionized industries the 44-hour week or less has become general, and in practically all, the working week is not more than 48 hours. This downward trend in the hours of labor will probably continue for a while. For example, a week of 40 hours or less is specified in most of the industrial codes of the NRA.

Education of the working classes in the proper use of leisure time has been woefully neglected, and even in the upper classes it is most inadequate. The result of the poor training and facilities for leisure is described in vivid, if exaggerated, terms by Nystrom:<sup>42</sup> "There is also the dangerous tendency with increasing leisure for individuals to become fat and flabby in mind as well as in body. The critics of leisure point to the menace of declining energy, ambition and ability among those whose leisure time is increased. This flabbiness and laziness is evident in both sexes, and may be seen in the growing tendency to ride instead of to walk, to participate in sports as spectators rather than as players and to shirk responsibility and effort in every form."

(e) *Increasing Urbanization.* Another aspect of our changing civilization, significant in relation to the increase in diabetes, is the growing concentration of population in cities, that has been fostered or imposed by the development of our present industrial organization. The trend toward the cities has resulted in cutting

down the expenditure of energy of large numbers of individuals. For example, the recreational activities of city dwellers tend to the passive types. For women, the removal to the city brings about a change to easier work, inherent in the differences between the city and country household. Again, transportation facilities and their use are much greater among urban residents. Differences in occupational patterns of the city and country need not be considered here because they have already been given their due weight. Moreover, the greater availability of concentrated foods, rich in calories, undoubtedly encourages overnutrition among urban residents. Urbanization, then, is a factor in the real increase in diabetes, and facts on the extent of this change are important.

In the United States, only 30 years ago, 60% of our people lived in the country, but today we are an urban people with only 44% of our population in rural areas. In the space of a generation the population of our cities has increased 125%, but our rural population has grown less than 20%. Moreover, the actual farm population in the country decreased in the decade 1920 to 1930. The increase in the rural population during the decade was limited to those residing in country villages. Because of the depression, many urban residents returned to their former homes in the country after 1930. Estimates of this movement run as high as 2,000,000 persons. This is, however, a purely temporary phenomenon and there is already evidence that the movement has again been reversed.<sup>43</sup>

TABLE 13.—GROWTH IN PROPORTION OF URBAN RESIDENTS\* IN PRINCIPAL COUNTRIES, 1900-1930.†

Country.	Per cent residing in urban areas.	
	1900.	1930.
United States . . . . .	40.0	56.2
Belgium . . . . .	52.3	60.5
Canada . . . . .	37.5	53.7
Denmark . . . . .	39.1	43.9
England and Wales . . . . .	77.0	80.3
Finland . . . . .	12.5	18.2
France . . . . .	40.9	49.1
Germany . . . . .	43.8	53.6
Netherlands . . . . .	70.3	78.8
New Zealand . . . . .	39.1	51.6
Norway . . . . .	28.0	28.5
Union of South Africa . . . . .	52.9	61.3

\* Definition of "urban" is not the same for all countries, although for each country comparable populations as of the two dates are used. In most cases, incorporated cities and towns are included; sometimes with a limitation as to size. In Belgium, Netherlands and Germany, communes over a certain size are included.

† Census data closest to these years. Most of the dates fall within 1 year. Exceptions are: 1930, France and New Zealand (1926), and Germany (1925); 1900, Union of South Africa (1904) and Netherlands (1909).

The long-time movement to the city is by no means limited to the United States. As Table 13 shows, cities throughout the world, almost without exception, have been growing faster than the country, and to a great extent at its expense. Generally speaking, this trend is greatest in the countries, particularly the British commonwealths, which have been developed latest. In England itself the change has been very small, but in this case the rural population had already diminished to about one-fifth of the total population three decades ago.

(f) *The Position of Women.* The greatly increased incidence of diabetes in women reflects to a great extent the gradual improvement in their position in modern times. This development is intimately related to the broad social changes already described, but the interest in it at this point is to review the effect on the actual physical work done by women. This has become progressively less in modern times, especially in industrial communities. Lower birth rates, which are a characteristic development all over the world, mean fewer children to work and care for. Smaller homes, epitomized by the small apartments of large cities, also have the effect of lessening work. Moreover, many of the former functions of the housewife—cooking, baking, food preserving, laundering and the making of clothing—are now largely carried on in industry. Whatever work remains in the home is rendered easier, as we have seen, by new domestic labor-saving devices. These are widely used in farm as well as in city homes. Another important development has been the great reduction in the number of domestic servants. Women who are dependent on their own earnings have come to prefer jobs in factories and offices, where work is easier, normally better paid and the hours are shorter. The effect of all these changes is, of course, not immediate, and none of them has yet exercised its maximum influence. For example, the decline in birth rates has been most rapid in recent years, and the women of childbearing ages of those years are only now approaching the “diabetes age.”

#### THE RECOGNITION OF DIABETES.

*The Influence of Medical Facilities on Its Differential Incidence.* The factors thus far discussed are those which make for real variations in the incidence of diabetes. Not all cases of the disease, however, are diagnosed, and the reported incidence must likewise be considered. In this, the extent and quality of medical services are the major items but, as indicated in the second paper,<sup>2</sup> differences in official statistical procedures in classifying deaths also play a part. In general, countries economically well off have better developed medical services than those less favorably situated, although this will not be uniformly true. Within all countries and regions, of course, the more prosperous classes have freer access to the best

medical facilities and make more frequent use of them than the lower economic and social groups. The chances of correct diagnosis of diabetes are then generally better for wealthier nations and classes.

Comparative data on the proportion of physicians and of beds in general hospitals to population in various countries and for several regions of the United States, presented in Table 14,<sup>44,45</sup> show that the diabetes rates are generally high in areas which have the greater number of physicians and hospital beds, and are low where the medical facilities are poorer. The correspondence is best in respect to hospital beds. Complete correspondence is not possible because of such factors as the differences in the quality, training and equipment of physicians in various areas, the development of socialized medicine in certain countries and the growth of specialized hospitals. In certain countries, furthermore, highly developed medical centers attract large numbers of foreign patients, Vienna being the prime example.

TABLE 14.—PHYSICIANS AND GENERAL HOSPITAL FACILITIES IN THE UNITED STATES AND ITS SUBDIVISIONS AND IN SEVERAL FOREIGN COUNTRIES.

Number of Physicians and of Beds in General Hospitals Per 10,000 Population.

Country.	Physicians per 10,000 population, 1929.	Beds per 10,000 population, 1928.
United States . . . . .	12.6§	37.0
New England . . . . .	13.6	50.5
Middle Atlantic . . . . .	13.6	
East North Central . . . . .	12.8	
West North Central . . . . .	13.1	37.5
South Atlantic . . . . .	10.8	
East South Central . . . . .	10.6	23.3
West South Central . . . . .	10.9	
Mountain . . . . .	10.8	19.7
Pacific . . . . .	17.3	
Great Britain . . . . .	12.2	47.8
Austria . . . . .	12.0†	
New Zealand . . . . .	9.1§	43.0
Switzerland . . . . .	8.4*	45.5
Denmark . . . . .	7.6	46.5
Germany . . . . .	7.4	49.9
Belgium . . . . .	6.8	59.0
France . . . . .	6.6	29.4§
Czechoslovakia . . . . .	6.5	24.3†
Norway . . . . .	6.1†	39.2
Netherlands . . . . .	5.6†	32.0†
Sweden . . . . .	3.8	25.4
Poland . . . . .	3.1†	2.1†

\* 1930. †1929. ‡ 1928. § 1927.

Urban and rural variations in the incidence of diabetes may likewise reflect, in part, differences in the medical facilities avail-



able. Everywhere physicians tend to congregate in the larger and more prosperous cities. There is constant complaint of the dearth of physicians not only in the country but even in the small towns outside the metropolitan zones. To some extent the situation today is better than appears on the surface, because modern transportation enables the small town and rural residents to avail themselves of urban medical services. At the same time physicians, both in town and country, serve a much wider area than formerly. Only in sparsely settled sections is the situation really bad.

*The Influence of Medical Progress on the Increase in Diabetes.* In like manner, developments in the field of medical service have tended to increase the number of recognized cases everywhere. In this connection, one must bear in mind that these improved medical services have become available to an increasing proportion of persons as a result of the concentration of populations in urban areas and because of improvement in transportation. In this country, the important change in the medical field is not an increase in the number but in the quality of physicians. The proportion of physicians to population has steadily dropped from 17.3 per 10,000 in 1900 to 12.6 in 1927.<sup>45</sup> This tendency is found in almost every section of the country. In most foreign countries, on the other hand, the proportional number of physicians has been growing.<sup>46</sup> (Table 15.) But everywhere there has been increasing emphasis on the quality of the candidates admitted to study and great improvement in the standards of medical education.

TABLE 15.—CHANGE IN THE RATIO OF PHYSICIANS TO POPULATION IN CERTAIN COUNTRIES, 1900–1925.\*

Country.	Physicians per 10,000 population.	
	1900.	1925.
Germany . . . . .	4.6	6.9
France . . . . .	4.9	5.9
Belgium . . . . .	5.3	6.2
Netherlands . . . . .	4.5	5.5
Sweden . . . . .	2.2	3.2
Norway . . . . .	5.0	5.5
Switzerland . . . . .	6.7	8.1
England and Wales . . . . .	7.0	6.4
Canada . . . . .	10.2	10.6

\* Data are those available closest to these years. Most of the dates fall within 2 years. Exceptions are: For 1900, France (1906) and Switzerland (1910); for 1925, England and Wales and Canada (1921) and Switzerland (1928).

Changes in the quality of the medical personnel are not measurable, but there are other significant statistical evidences of improvement in medical care. For example, in the 30 years between 1900 and 1930 the number of hospitals in the United States increased

from 2070 to over 6500\* and the number of hospital beds even more.<sup>47,48</sup> This increase in hospital facilities extended to every type. The number of beds per 10,000 population in general hospitals rose from 25.8 in 1925 to 31.3 in 1932. There was a negligible decline in 1933. The *per capita* expenditure of cities of 30,000 and over for these hospitals increased over 3 times between 1913 and 1928 and 5 times between 1903 and 1928.<sup>49</sup> The number of general hospitals with outpatient departments rose from 703 in 1921 to 1562 in 1931, and every section of the country benefited from this increase. The number of clinics of all types grew from about 150 in 1900 to 3944 in 1921 and 7595 in 1931.<sup>50</sup> The extent to which all these clinics are used is not available, but the number of visits reported in 24 of the 25 largest cities of the country increased from 7 millions in 1921 to nearly 14 millions in 1931. Between 1927 and 1931 alone, there was an increase in the number of visits to outpatient departments in this country from nearly 14 millions to 23.5 millions. Finally, there has been a rapid growth in the number of private clinical laboratories.

Similar expansion of hospital facilities has been going on in many countries. No systematic collection of data on this matter exists, but the facts for a few countries clearly show the trend. In Germany, for example, the number of beds in general hospitals rose from 29 per 10,000 population in 1900 to 55 in 1926, and in Sweden, from 21.6 in 1900 to 39.6 in 1926. In France, the number of hospitals increased 15.1% and the number of persons treated 74.3% between 1900 and 1930, while the population showed an increase of only 6.4%. In Switzerland, the number of hospitals increased 51% between 1916 and 1930 and the number of admissions 55%, while the population increased only 6.2%.

The growth of industrial medical services has also favored more frequent diagnosis of diabetes in recent years. In 1930-1931, 5564 plants, with 4,200,000 employees, were known to provide some form of medical service.<sup>51</sup> More than one-half these plants, employing 3,100,000, required medical examination prior to employment, and periodically thereafter. These examinations often include an urinalysis and, when necessary, a blood sugar estimation. Consequently, an increased number of diabetics has been discovered in this manner. Moreover, many modern plants do not limit their medical services to examinations or first aid. At the time of the survey just quoted, 773 industrial plants employed 617 full-time physicians and 518 on part time for the medical care of their employees, numbering about 600,000. In no less than 515 plants with 430,000 employees, medical care was extended to the workers' families.

\* In recent years the number of hospitals has been declining, but this is partly due to amalgamation of previously existing units. The number of hospital beds has continued to increase.

Another development which has increased the chance of a correct diagnosis of diabetes is the growing frequency of medical examination of supposedly healthy persons. The most important factor in this situation in the United States is the vast growth of life insurance in recent decades, examinations for which have long included a routine urinalysis. Distinct advances have been made in the technique and its standardization in the large biochemical laboratories of the life insurance companies. In recent years the number of blood sugar estimations for life insurance examination has also been growing rapidly. This trend will be accelerated by the method, developed 3 years ago, of preserving small samples of blood so that blood sugar estimations of samples taken by medical examiners in the field can be made by a standard technique at home office laboratories. The importance of life insurance in this matter in the United States may be realized from the number of persons applying for life insurance requiring medical examination, which has reached the figure of 4 millions in some recent years and even today is about 3 millions per year. More direct evidence of the place of life insurance in the identification of diabetes is that 15.9% of all Joslin's male patients of insurable age were discovered in this manner and, of the cases seen between 1920 and 1928, actually 17.7%. In view of the particularly sharp advance in the incidence of diabetes in women, it is significant that the number of women applying for life insurance has been increasing at a much faster rate than of men. For example, in 1900 women constituted, only 7.6% of all "Ordinary" applicants in the Metropolitan Life Insurance Company, but in 1930 the proportion was 26.9%. In these 30 years, which witnessed a tremendous growth in life insurance, female applicants in the Company increased by over 80 times, while male applicants increased by about 20 times. That life insurance is a factor in the increased recognition of diabetes in many other countries also may be inferred from the growth in the *per capita* amount of insurance in force, especially during the past decade.<sup>52</sup>

Similar in its nature and significance is the growing popularity of periodic health examinations. Life insurance companies have done much to foster this development, even to the extent of paying for the examination of their policyholders. That this is not a matter of slight importance may be realized from the fact that over 100,000 policyholders of the Metropolitan Life Insurance Company alone took advantage of this service in 1933. Since 1920, their number has grown tenfold. The number of individuals receiving periodic examinations from their personal physicians must also be very large today, due to the persistent efforts of medical societies to popularize the idea of periodic physical examination.

Certain other advances in the field of medicine, even if their effects are as yet not measurable, are nevertheless significant in regard to diabetes. On the one hand, there have been distinct

advances in the techniques involved in the diagnosis of diabetes. While tests for urinary glycosuria are not new, the methods in use at the present time are of relatively recent origin. This is even more true of cheap and accurate tests for blood sugar, particularly of micro methods. Moreover, routine examination, even of urines for sugar, is relatively recent. Bolduan<sup>53</sup> has shown that even in a high-grade institution like New York Hospital, this did not become the practice until some time between 1880 and 1890. Routine blood sugar estimation has not been done in many hospitals for more than a few years, and even today is not widely done. The increased use of diagnostic aids is also in part the result of changes in the training and personnel of the medical profession. The passing years have brought in a new type of physician, trained from the beginning in the use of modern diagnostic techniques and thus accustomed to use them more freely than the older generation of physicians.

These advances are not limited to any one country. The wide and rapid diffusion of scientific knowledge makes new techniques available within a relatively short time to physicians in all parts of the civilized world. Modern industrial methods make possible the manufacture of new equipment at prices which soon bring it within the reach of hospital groups and physicians everywhere. Modern methods of organization promote frequent use of these facilities, thus bringing down the unit costs to relatively modest figures.

These changes in the medical field have come about during an era in which there has also developed a new and franker attitude toward the body and its functions. This has been especially true in regard to women. For this reason greater attention has been directed toward their medical needs, and the medical services rendered to them have increased. This also has aided in the discovery of more cases of diabetes.

*Other Factors in the Increasing Incidence of Diabetes.* An apparent increase in diabetes has resulted from the steady growth in the proportion of old persons in the population and especially of older women,\* among whom diabetes is most frequent. Increase from this source is viewed as apparent because it occurs without any change in the specific age and sex rates of incidence of diabetes. Table 16 shows that the growth in the proportion of older persons is characteristic of almost all civilized countries.<sup>54,55</sup> In the United States, for example, the number of persons aged 45 and over constituted 22.8% of our population in 1930, compared with only 18.9% in 1910 and 17.7% at the beginning of the century. Stated in another way, the number of people in the United States at ages past 45 has

\* In our discussion of diabetes death rates, the effect of these factors was discounted in comparisons of rates adjusted for changes in sex and age—not, however, in crude death rates which were of necessity more frequently used.

more than doubled in the last 30 years, while the total population has grown by only 62%. The increase in the number of older women is even greater.

TABLE 16.—THE INCREASING PROPORTION OF OLDER PERSONS AND OF OLDER WOMEN IN THE POPULATION OF PRINCIPAL COUNTRIES, 1900–1930.\*

Country.	Percentage of population.					
	Persons.				Females.	
	Ages 40 and over.		Ages 60 and over.		Ages 40 and over.	
	1900.	1930.	1900.	1930.	1900.	1930.
United States . . . . .	23.4	29.4	6.4	8.5	11.1	14.2
Australia . . . . .	21.9	31.1	6.2	9.4	9.5	15.3
Belgium . . . . .	27.9	33.2	9.5	10.3	14.4	17.1
Canada . . . . .	24.5	28.5	7.7	8.4	11.7	13.2
Denmark . . . . .	28.4	31.7	9.8	10.8	15.0	16.6
England and Wales . . . . .	25.3	35.7	7.4	11.4	13.4	19.3
Finland . . . . .	26.9	30.3	8.2	9.4	14.2	16.1
France . . . . .	35.1	38.5	12.5	13.8	18.2	20.6
Germany . . . . .	25.7	33.3	7.8	10.4	13.6	17.7
Ireland . . . . .	29.0	33.3	10.9	12.3	15.0	16.7
Italy . . . . .	29.1	30.3	9.6	10.8	14.8	15.9
Netherlands . . . . .	26.8	29.1	9.2	9.4	13.8	14.9
New Zealand . . . . .	22.7	31.9	6.7	8.7	9.5	15.4
Norway . . . . .	28.4	30.8	10.8	11.6	15.3	16.6
Spain† . . . . .	28.2	29.1	8.2	9.5	14.0	15.3
Union of South Africa‡ . . . . .	17.0	26.0	3.4	7.1	7.1	12.3

\* Data relate to censuses closest to these years. Most of the dates fall within 1 year. Exceptions are, for 1930, Ireland and France (1926) and Belgium and Spain (1920); for 1900, Union of South Africa (1904).

† Ages 41 and over and 61 and over.

‡ European population.

A real increase in the number of diabetics in recent years has also come about as a result of the prolongation of life of diabetic patients, chiefly through the use of insulin. In a later paper, we shall show how great has been the actual reduction in the death rate of diabetics, which is, of course, quite a different thing from the death rate from diabetes in the general population. The net result of the recent advances in therapy has been to increase the number of diabetics living at every age, but most of all at the younger ages.

While we do not lay much stress on racial susceptibility, a possible factor in the increased frequency of diabetes in some areas is the rapid growth of race stocks with a higher than average incidence of diabetes. Thus, the number of Jews in the United States has increased nearly fourfold in a generation—from slightly more than 1 million in 1900 to over 4 millions at the present time.<sup>56</sup> For the

country as a whole, the item is not a large one. Jews constituted 1.3% of our population at the beginning of the century and even today, only 3.2%. This influence is much more important in a city like New York, where the number of Jews has risen in the past 30 years from 600,000 to over 2 millions.<sup>57</sup> Moreover, the growth resulted largely from immigration of young people who are only now beginning to be represented in large numbers in those older age groups where the mortality from diabetes is highest. The Jews are singled out for specific mention because of the interest in their high incidence of diabetes. The same thing applies in lesser degree to some other racial groups. This factor, if at all important, is significant only in countries which have been growing by immigration, but not in the more settled countries.

**Summary and Conclusions.** Overweight is the most common factor in the etiology of diabetes. The evidence shows that variations in diabetes mortality, whether from the point of view of regional or social distribution, or from the point of view of changes in time, are associated with environmental conditions which influence the frequency of overweight. Thus, diabetes is found to be most prevalent among persons whose work requires the expenditure of relatively little physical energy and who have higher than average incomes. Likewise, the disease tends to be most frequent in societies in which "real" incomes, as measured by purchasing power of wages, are highest and the proportion of persons engaged in light work is greatest. These basic conditions also explain the real increase in diabetes throughout the world. The rapid expansion of the use of machines driven by mechanical power has made industrial workers mere tenders of machines, has lightened the burden of farm workers, transferred large numbers into clerical and sales jobs and reduced hours of labor. The amount of energy expended in work, therefore, has been drastically cut down for the majority of the working population. The growth of urban areas, often at the expense of the country, has made ever larger numbers subject to these influences. Concomitant with these developments, if not as a result of them, an increase in "real" wages has occurred. Consequently, at the same time that individuals have been called upon to work less hard, thus reducing food requirements, they have become able to buy more food. Either condition alone would favor an increased frequency of overweight and, therefore, of diabetes. Together their power is greatly enhanced to bring about the pathology we call diabetes.

As for women, the very great increase in diabetes among them reflects the betterment in their social position. They have shared in the benefits of the increasing family income. Domestic labor has been lightened by the decreased size of the family, by the transfer of many domestic functions to industry and by the use of

labor-saving devices in the home. Moreover, employed women have tended to drift into less arduous jobs. Increasing attention to the medical needs of women has also undoubtedly resulted in the more frequent recognition of diabetes among them.

Another factor in the differential incidence of diabetes is the quality and efficiency of medical service. Diabetes rates are generally highest where either medical facilities, as measured by hospital beds to population, are most abundant, or physicians in proportion to population, most numerous. More frequent discovery of the disease, causing an apparent increase in its incidence, has followed an increase in medical facilities, widespread improvement in medical education and important advances in diagnostic methods. These methods have become increasingly familiar to the average physician, largely as a result of the gradual replacement of the older members of the profession by younger men trained from the beginning in these newer techniques. At the same time, these procedures have been used on a vastly increased scale as a result of their routine use in hospitals and the medical examination of large numbers of supposedly healthy persons for insurance and health purposes. Modern medical service has become available to an ever increasing proportion of the population as a result of the concentration of populations in urban areas.

The rise in the incidence of diabetes also reflects the great change in the constitution of populations. Everywhere the proportion of persons in middle and later life, among whom diabetes is most frequent, has been steadily increasing. Especially is this true of older women. Another factor, significant in certain areas, is the differential increase of race stocks which seem to be especially susceptible to the disease. A third item not to be overlooked is that the improvement in diabetes therapy, largely as a result of insulin, has itself increased the number of diabetics living.

The increase in the incidence of diabetes is only in part a real one. Such is the increase resulting from environmental changes which favor frequent overnutrition and also that following the reduction in the mortality of diabetics due to insulin. On the other hand, the increase in diabetes due to the growing proportion of older persons is not a problem to give concern, because the sex and age characteristics of the disease make it inevitable. The rest of the apparent increase in diabetes incidence results largely from the identification of cases which formerly escaped attention. Not one new case of the disease is added to the true number by improvement and more frequent use of medical facilities. The question naturally arises as to the relative importance of the several factors mentioned—how much of the increase in diabetes is real, and how much apparent. In the present state of our knowledge, however, it is impossible to give a definite answer to this question.

It is likely that the incidence of diabetes will continue to grow and diabetes death rates likewise to increase moderately for several years, until the forces described in this paper reach equilibrium. Advances in industrial technology are still being made. Consequently, the productivity of workers may be expected to increase; mechanical power to displace human labor to a greater extent than today, both in industry and agriculture; and standards of living to rise. As a result, a further real increase in diabetes will occur unless we are more successful than we have been in educating the public as to the dangers of overweight and how it may be prevented. Some further growth in the number of diabetics may be expected as a result of further increase in the average age of the population, which will not become stationary for several decades. The recognition of the disease will also be more frequent in the future because of improvements, still being made, in the efficient use of our medical resources and in diagnostic techniques.

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## THE ACTION OF THEVETIN, A CARDIAC GLUCOSID, AND ITS CLINICAL APPLICATION.\*

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THE plant *Thevetia neriifolia* (Jussieu) is indigenous to South America and the West Indies, but is now cultivated in the East Indies, India, the Hawaiian Islands and West Africa, chiefly for ornamental purposes. It belongs to the family Apocynaceæ, which also gives rise to apocynum (*A. cannabinum* or *A. androsæmifolium*), oleander (*Nerium oleander*) and different species of *strophanthus*. *Thevetia neriifolia* is a tree 10 to 20 feet high, and bears fruits which finally yield dark brown, hard-shelled nuts, as shown in Fig. 1.

The kernels of these nuts have been known to be poisonous to men and animals since the latter half of the sixteenth century. Cases of poisoning have been described by Decourtilz,<sup>1</sup> Balfour and MacLagen,<sup>1</sup> Dumontier,<sup>2</sup> and Dey.<sup>3</sup> Various colloquial names have been assigned to the nuts according to the localities, being called be-still nuts in the Hawaiian Islands, ahouai in the Antilles, joro-joro in Dutch Guiana, lucky seed in Jamaica, cascaveleira in Brazil, bois saisi in Haiti, and pilakanir or kokilphul in India.

The first chemical study on the nuts of *Thevetia neriifolia* was undertaken by DeVry,<sup>2</sup> in 1863, who isolated from them a glucosid and named it thevetin. In spite of subsequent investigations, as carried out by Blas,<sup>4</sup> Weitz and Boulay,<sup>5</sup> Ayyar,<sup>6</sup> Chopra and Mukerjee,<sup>7</sup> and Ghatak,<sup>8</sup> the chemistry of thevetin is still in a realm of uncertainty and needs further exploration.

Husemann,<sup>1</sup> in 1876, showed that thevetin has a digitalis-like action on the heart, but he believed that it caused abscess formation upon injection. Chopra and Mukerjee<sup>7</sup> recently made an extensive pharmacologic study on thevetin and concluded that "the margin between the therapeutic and toxic limits seemed to be too low to warrant its safe administration." They did not determine the

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exact potency of the principle by any of the well-known assay methods.

Our interest in thevetin was initiated by one of us (H.L.A.)<sup>9</sup> when a child, aged 5 years, died 20 hours after eating the nuts, at the Children's Hospital, in January, 1931. The manifestations were like digitalis poisoning. It also happened that several chickens

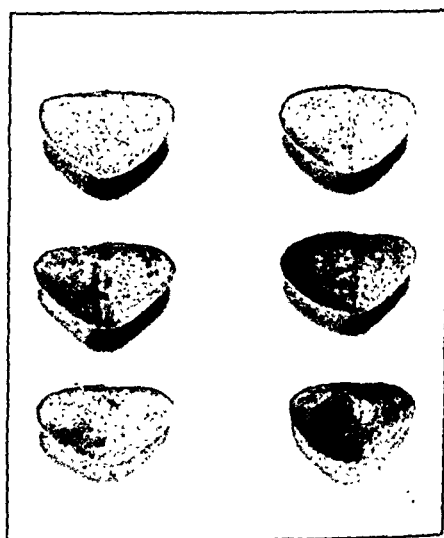


FIG. 1.—Upper, tree of *Thevetia neriifolia*; lower left, flower; lower right, mature nuts.

succumbed from the same cause at this child's home. A sample of the nuts was soon collected and forwarded (for chemical investigation) to the laboratory with which another one of us (K. K. C.) is associated. Chen and Chen<sup>10</sup> ultimately isolated thevetin and subsidiary glucosids in pure form, and subjected them to a quantitative pharmacologic evaluation.<sup>11</sup>

**Laboratory Data.** Thevetin is soluble in alcohol and less in water. It melts at about 193° C. (corrected) and has a specific rotation of  $[\alpha]_D^{28} -62.5^\circ$ . Its empirical formula is  $C_{29}H_{46}O_{13} \cdot 2H_2O$ . The substance is relatively stable, since a dilute aqueous solution retains its physiologic activity for more than a year.

**Action on the Heart.** The chief action of thevetin is on the heart. In frogs it causes systolic ventricular standstill either by injection into the lymph sac or by perfusion into the inferior vena cava. On the mammalian heart, Chopra and Mukerjee<sup>7</sup> observed that thevetin has a stimulant action in small amounts, but depresses and stops the ventricles in large doses. During stimulation the cardiac output and coronary outflow are both increased; but the latter diminishes when intoxication by larger doses of thevetin begins. Electrocardiograms, recorded from etherized cats while a dilute solution of thevetin was slowly injected, showed typical changes of digitalis-like action<sup>11</sup> such as bradycardia, inversion of *T* wave, *P-R* prolongation, *A-V* dissociation, ventricular tachycardia and, finally, ventricular fibrillation. In terms of the fatal dose, it appears to take a relatively smaller quantity of thevetin to produce the first appearance of *P-R* prolongation and maximal slowing of the heart rate than for ouabain or digitoxin.

Thevetin has a persistence of action comparable to that of ouabain as determined in cats. Of the fatal dose, 47% may remain in circulation for more than 5 hours, and 71% for more than 22 hours, but 82% may be completely eliminated in 24 hours. Hatcher<sup>12</sup> reported that in cats, digitalis and digitoxin might be present in the body for a full month, while the largest sublethal doses of strophanthin disappeared in a day.

In animals, thevetin is easily absorbed when it is given per os or by subcutaneous injection.

**Potency.** When assayed by the method of Hatcher and Brody,<sup>13</sup> the cat unit of thevetin is determined to be 0.85 mg. per kg.<sup>11</sup> With the U. S. P. frog method,<sup>14</sup> the glucosid has a minimal systolic dose of 0.004 to 0.005 mg. per gm. Ouabain assayed under the same laboratory conditions is shown to have a cat unit of 0.12 mg. per kg. and a minimal systolic dose of 0.005 to 0.006 mg. per gm. in frogs. Based upon the cat unit, thevetin is  $\frac{1}{7}$  as toxic, but also  $\frac{1}{7}$  as powerful, as ouabain.

**Action on Other Organs.** Aqueous solutions of thevetin are bitter to the taste. Like other cardiac glucosids, thevetin, in large doses,

causes a sustained rise in blood pressure with occurrence of vagal pulse, arrhythmia and tachycardia, as shown in Fig. 2. It induces nausea and vomiting in pigeons, cats or dogs. Thevetin in appropriate concentrations stimulates intact or isolated intestines, uteri and urinary bladder,<sup>7,11</sup> the action probably being on the smooth muscles.

With aseptic precautions, no necrosis occurs when thevetin is injected, either in rabbits or in men, intradermally, subcutaneously or intramuscularly.<sup>11</sup> Like other digitalis glucosids, it may produce a slight pain at the point of injection, but it does not cause abscess formation, as claimed by Husemann.<sup>1</sup>

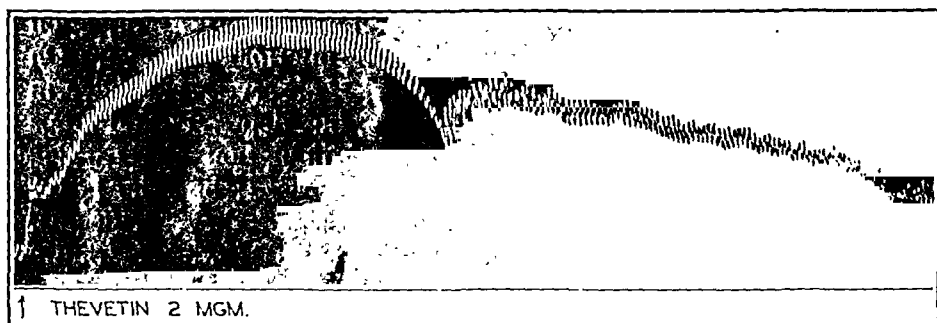


FIG. 2.—Action of thevetin on blood pressure. Cat, male, weighing 2.66 kg., was decerebrated and pithed. Both vagi were sectioned. Artificial respiration was administered. The injection of thevetin was made by the intravenous route.

*Action of a Single Dose of Thevetin in Men With No Apparent Cardiac Disorders.* In view of the fact that thevetin is sufficiently soluble in water, relatively stable in solutions, easily absorbed, and prompt in action, it appeared justifiable to study its action in men. Although it is less persistent than digitalis, it has at the same time less risk of cumulative action.

Upon the oral administration of thevetin to normal individuals in doses of from 1 to 5 cat units, there regularly occurred a fall in the pulse rate (Table 1, Cases 1 to 5). The degree of this fall, which ranged from 9 to 20 beats per minute, bore no direct relation to the dosage. The greatest decrease in pulse rate occurred with 2 cat units, whereas the least was with 4 cat units. A maximal effect in this direction was recorded in 2 to 3 hours; but again the time factor was not directly related to the dosage. Interestingly, heart burn was occasioned in both instances where the dose of thevetin exceeded 3 cat units in the normal subjects.

One individual (Table 1, Case 6) received 3 cat units of thevetin intramuscularly with a resultant decrease in the pulse rate of 12 per minute after 3 hours. He experienced no general subjective manifestations, but there was a dull ache at the site of injection for about 5 hours. The discomfort gave way to slight tenderness at

TABLE 1.—EFFECTS OF A SINGLE DOSE OF THEVETIN AND TINCTURE OR POWDER OF BE-STILL NUTS.

Case.	Age.	Sex.	Weight, pounds.	Diagnosis.	Funct. capacity.	Before.		Preparation.	Dosage, cat units	Route.	Interval, min.	Objective results.			Subjective results.	Adverse reactions.
						P.	B.P.					P	B.P	EKG		
1	36	M	..	No cardiovascular diagnosis	I	92	...	Powder	?	Oral	150	-20	..	..	..	0
2	35	M	..	No cardiovascular diagnosis	I	84	...	Powder	1	Oral	180	-17	..	..	..	0
3	23	M	..	No cardiovascular diagnosis	I	84	...	Powder	3	Oral	180	-12	..	..	..	0
4	26	M	..	No cardiovascular diagnosis	I	64	...	Powder	4	Oral	150	-9	..	..	..	Heart burn.
5	34	M	..	No cardiovascular diagnosis	I	76	...	Powder	5	Oral	150	-13	..	..	..	Heart burn.
6	34	M	130	No cardiovascular diagnosis	I	76	...	Thevetin	1	I.M.	180	-12	..	..	..	Dull ache at site of injection.
7	26	M	156	No cardiovascular diagnosis	I	76	...	Thevetin	1	I.M.	92	-50	..	..	..	Burning, throbbing neuritic pain.
8	41	M	150	Rheumatic heart disease	III	84	130/?	Thevetin	2.5	I.V.	10	-6	2/?	..	Breathes easier	0
9	60	M	96	Arteriosclerotic heart disease	III	102	156/130	Thevetin	5	I.V.	13	-10	+10S -4D	..	..	0
10 <sup>a</sup>	18	M	165	Rheumatic heart disease (in fibrillation)	III	90	110/?	Thevetin	5	I.V.	13	-32	-2/?	+	Less pounding	0
10 <sup>b</sup>	..	M	190	Rhythm normal	III	100	110/86	Thevetin	5	I.V.	39	-40	..	..	..	0
11	62	M	165	Arteriosclerotic heart disease (parox. tachycardia)	III	146	110/84	Thevetin	5	I.V.	45	0	-12S	0	..	0
12	47	M	165	Lactic acidosis with regurgitation	III	84	...	.....	5	I.V.	20	-20	-9D	..	..	More extrasystoles
13	29	M	130	Chronic nephritis with hypertension; myocard. degeneration	III	118	172/132	Thevetin	5	I.V.	..	0	..	..	..	Nodal rhythm with many extrasystoles.
14	62	M	190	Arteriosclerotic heart disease	III	84	122/?	Thevetin	5	I.V.	10 hr.	-12	-14/?	+	+	0
15	47	M	210	Arteriosclerotic heart disease	III	94	154/?	Thevetin	5	I.V.	100	-10	-12/?	+	+	0
16	41	M	143	Rheumatic heart disease	II <sup>a</sup>	72	130/88	Thevetin	5	I.V.	20	-8	-6D	+	+	0
17	53	M	132	Rheumatic heart disease	II <sup>b</sup>	98	96/70	Thevetin	5	I.V.	40	-2	+16S	+	+	0
18	43	M	130	Rheumatic heart disease	II <sup>b</sup>	68	112/?	Thevetin	5	I.V.	19	-12	+10D	+	+	0
19	66	M	180	Arteriosclerotic heart disease	III	108	112/?	Thevetin	5	I.V.	90	-12	0	+	+	0
20	76	M	140	Arteriosclerotic heart disease	III	84	200/120	Thevetin	5	I.V.	4 hr.	-8	0	+	+	Diuresis
21	70	M	139	Arteriosclerotic heart disease	III	84	198/120	Thevetin	5	I.V.	90	+	..	+	+	0
22	57	M	146	Arteriosclerotic heart disease	III	76	110/?	Tincture	2	Oral	..	0	..	+	+	0
23	37	M	140	Rheumatic heart disease	II <sup>b</sup>	76	85/?	Tincture	1.3	Oral	Indef.	-16	0	0	0	0
24	61	M	151	Arteriosclerotic heart disease	III	76	85/?	Tincture	0.5	Oral	..	0	0	0	0	0
25	61	M	187	Arteriosclerotic heart disease	III	56	155/?	Tincture	0.6	Oral	..	0	0	0	0	0
26	73	M	200	Arteriosclerotic heart disease	III	124	174/?	Tincture	0.6	Oral	Indef.	-18	0	0	?	0
27	42	M	142	Arteriosclerotic heart disease	II <sup>b</sup>	80	130/60	Solution	0.5	Oral	..	0	0	+	+	0
28 <sup>a</sup>	65	M	118	Thyrototoxic heart disease	II <sup>b</sup>	72	170/?	Solution	0.5	Oral	Indef.	-8	0	0	0	0
28 <sup>b</sup>	..	M	..	..	..	92	170/?	Tincture	0.5	Oral	..	0	0	0	0	0
29	56	M	140	Rheumatic heart disease	III	92	120/?	Tincture	1.6	Oral	12 hr.	-12	0	+	+	0
30	43	M	239	Rheumatic heart disease	II <sup>b</sup>	72	140/?	Solution	0.6	Oral	..	0	0	0	0	0

the end of 5 hours. A second individual (Table 1, Case 7) was given 5 cat units of thevetin intramuscularly. The pulse rate began to decline 17 minutes after the injection into the left deltoid and reached its maximal slowing of 20 beats per minute in 92 minutes. Burning, shooting neuritic pains with muscular twitching developed in the left arm and persisted with some abatement throughout the day. On the following day there remained only slight residual tenderness at the site of injection.

*Action of a Single Dose of Thevetin and Other Preparations of Be-still Nuts in Patients With Cardiac Disease.* With the safe background of pharmacologic support, it was deemed wise not to exhaust the study of the normal subject in his responses to the derivatives of be-still nuts but to proceed immediately to the logical clinical application of these substances in the treatment of cardiac affections.

Since poisoning has occurred by eating be-still nuts, it becomes apparent that thevetin is easily absorbed from the gastro-intestinal tract. This is well borne out by the results of animal experiments. Studies were, therefore, carried out by either intravenous injection or oral administration of pure thevetin. For the latter purpose, a solution of thevetin in 65% alcohol by volume was prepared. In addition, a tincture of the defatted kernels and the powder of the same (dispensed in capsules) were employed by mouth. Each preparation was so standardized (physiologically) that each cubic centimeter or capsule was equal to 1 cat unit.

To test the influence of a single dose of these products, 25 observations were made upon 23 patients with a variety of cardiovascular diseases. The results are grouped in Table 1. It will be observed that with a single exception (Case 8), the intravenous injections of thevetin were in doses of 5 cat units, whereas the alcoholic solution of thevetin and tincture of Thevetia were given orally in doses of 0.5 to 2 cat units. Accordingly deductions must be drawn separately and with due consideration for the discrepancy.

A fall in pulse rate succeeded the intravenous administration of a single dose of thevetin in 12 of 15 instances (14 patients). No decrease occurred in 2 and a rise was observed in 1 patient. The maximal fall appeared in less than 45 minutes in 9 observations. This point was deferred to 10 hours in 1 instance. The degree of pulse fall ranged from 2 to 40 beats per minute. As evidence that the cardiac rhythm played no decisive rôle in this direction among these patients may be cited Case 10. When the normal rhythm was restored in this patient, a greater response to 5 cat units of thevetin was observed than during a period of auricular fibrillation (40 as compared with 32). The blood pressure changes were equivocal; but the circumstance of equal numbers (4) with a fall in systolic blood pressure as with a rise should be remarked. Three patients showed no effect and 1 (Case 16) had a fall in diastolic pressure only. Of 14 patients, 13 showed some electrocardio-

graphic changes. The details of this phase of the study will be elaborated in the consideration of the treatment of cardiac decompensation, but in this connection it should be noted that only 2 patients (Cases 12 and 13) showed adverse results to a single dose of thevetin administered intravenously, and both of these had extrasystoles. Case 13 will demand further discussion, because of serious faults in conduction that attended the continued use of thevetin. Subjective improvement after a single dose of thevetin was volunteered by 3 patients and included relief of dyspnea, quieter cardiac activity and diuresis.

Tincture of Thevetia and the alcoholic solution of thevetin were administered to 9 patients (10 observations). The dosage was so small (0.5 to 2 cat units) that it is not surprising to note only 4 instances of lower pulse rate and 2 of altered electrocardiograms in response to isolated doses by mouth. One patient volunteered the statement of relief of dyspnea. Actually the interest in this limited group of patients rests in other directions which receive later consideration.

*Action of Thevetin and Other Preparations of Be-still Nuts in Cardiac Decompensation.* In Table 2 the results of the treatment of cardiac decompensation have been analyzed. Twenty-three patients comprised the group, which includes such patients from Table 1 (Case 8 on) as suffered from cardiac decompensation. In general, they represent the usual run of patients admitted to a general hospital for this condition. Their etiologic background covers the commoner causes of chronic myocardial degeneration, and the selection of subjects was based only upon the exclusion of definitely digitalized patients. Two of the group had been on maintenance levels of digitalis. Twenty-five periods of observation were available upon the 23 patients. In all patients tolerance was estimated upon body weight, and in the average instance theoretic tolerance was sought in 5 days. Regardless of the preparation or the route of administration, the cat unit equivalent served as the standard of dosage. The individual dose of thevetin never exceeded 5 cat units nor the daily total 10 cat units.

Insofar as the pulse response was concerned, 13 to 14 patients receiving thevetin intravenously showed slowing of the rate of from 2 to 52 beats per minute. These figures represent the radial pulse rates. The apical rates were likewise slowed and, as a rule, the pulse deficit in auricular fibrillation materially reduced. A single patient suffering from auricular paroxysmal tachycardia (Case 11) showed no fall in the pulse rate. With the oral preparations, tincture of Thevetia and the alcoholic solution of thevetin, a slowing of the pulse, ranging from 4 to 48 beats per minute, was observed in 8 of 9 patients. With 3 exceptions (Cases 22, 26 and 29), the doses of these oral preparations were relatively small or they were utilized for the maintenance of circulatory balance (Fig. 3).



TABLE 2.—ANALYSIS OF THE EFFECTS OF THEVETIN OR TINCTURE OF BE-STILL NUTS ADMINISTERED IN CARDIAC DECOMPENSATION.

Case.	Diagnosis.	Time decomp.	Recent digitalis.	Rhythm.	Funct. capacity.	Wt., pounds.	Before.				Prepara- tion.	Dosage, cat units.		Interval.	Objective results.								Subjective results.	Adverse reactions.			
							P.	B.P.	V.P.	P-R.		T.	S-T.		P-R.	T.	S-T.	Q-R-S.	Rhythm.	Mis- cell.							
8	Rheu. heart dis.	4 mos.	Maintenance	Aur. fibr.	III	150	84	130/7	16	..	1,2	1,2	✓	✓	10 min.	2 5' I.V.	Thevetin	0	2?	0	..	0	+	0	0	Less dysp.	0
9	Art.scler. heart dis.	3 wks.	None	Occas. extrasys.	III	96	102	156/130	12	0.16	All	1	✓	✓	13 min.	5' I.V.	Thevetin	-3	+10 S -4 D	-10	+	0	0	0	0	0	0
10a	Rheu. heart dis.	5 mos.	Irreg.	Aur. fibr.	III	165	90	110/7	..	..	1	✓	✓	✓	13 min.	5' I.V.	Thevetin	..	-2?	-32	..	1	0	0	Less	0	
10b	Rheu. heart dis.	5 mos.	Irreg.	Regular	III	165	100	110/86	..	..	=	✓	✓	✓	39 min.	5' I.V.	Thevetin	..	..	-40	..	✓	0	0	pounding	0	
11	Art.scler. heart dis.	7 mos.	None	Aur. fibr., then aur. tachycar.	III	190	146	110/84	..	0.17	1	✓	✓	✓	34 hrs.	10 I.V.	Thevetin	..	-12 S -9 D	0	0	0	0	0	0	0	0
12	Luetic heart dis.	15 mos.	None	Complete block; extrasys.	III	165	84	..	12	..	2,3	✓	✓	✓	20 min.	5' I.V.	Thevetin	..	..	-20	..	0	0	0	0	0	Incr. extrasys.
13	Chronic nephritis with hypertension; myoc. degeneration	6 wks.	Indef.	Occas. extrasys.; bun-br. block	III	130	118	172/132	18	..	..	..	✓	✓	47 hrs.	15 I.V.	Thevetin	-2	-18 S -72 D	-52	..	✓	+	Most bi- zarr	0	0	Remark. arrhythmia; disappeared in 6 days.
14	Art.scler. heart dis.	9 mos.	None	Aur. fibr.	III	190	84	122/7	..	..	..	..	✓	✓	2 days	15 I.V.	Thevetin	..	-14 S 7 D	-18	..	..	+	..	0	0	
15	Art.scler. heart dis.	12 yrs.	Irreg.	Many extrasys.; bun-br. block	III	210	90	154/7	16	0.14	All	1,2	✓	✓	12 days	37.5 I.V.	Thevetin	-2	+10 S 7 D	-8	+	1	+	0	0	0	Cramps and diarrhea for 1 day; not continued.
16	Rheu. heart dis.	2 yrs.	None	Regular	IIa	143	72	130/88	10	0.20	3	✓	✓	✓	3 days	20 I.V.	Thevetin	-2	..	-4	+	+	+	0	0	0	0
17	Rheu. heart dis.	14 mos.	None	Regular	IIb	132	98	96/70	12	0.13	3	✓	✓	✓	40 min.	5' I.V.	Thevetin	-1	+16 S -10 D	-2	+	0	0	0	0	0	0
18	Rheu. heart dis.	2 mos.	Indef.	Aur. fibr.; many extrasys.	IIb	130	68	112/7	13	..	All	1,2	✓	✓	25 hrs.	15 I.V.	Thevetin	0	..	-22	..	0	0	0	0	0	More extrasys.; died after 3d in jection.

19	Art.scler. heart dis.	5.5 cc. of tincture	2 yrs.	III	180	108	14	1, 2	1, 2	..	Thevetin	30	I.V.	5 days	-44	..	0	0	Diuresis	Marked impr. in edema and dyspnea decreased	0
20	Art.scler. heart dis.	Little infusion	9 mos.	III	140	96	110/104	0.17	1, 2	1, 2	Thevetin	30	I.V.	6 days	-36	-6S -14D	+	1	Diuresis	Anorexia; diarrhea without cramps 1 day; disappeared.	0
21	Art.scler. heart dis.	None	4 1/2 mos.	III	139	84	108/120	0.18	1	1	Thevetin	20	I.V.	4 days	-30	-3S -20D	+	+	Diuresis	Anorexia and abd. discomfort with diarrhea on 5th day.	0
22	Art.scler. heart dis.	None	2 1/2 yrs.	III	146	76	110/76	0.14	1	1	Tincture	22	O.	4 days	-20	-10S 7D	+	0	Slight diuresis	Diarrhea 2d day; nausea, emesis 4th day; more extrasy.	0
23	Rheu. heart dis.	Small doses for 2 yrs.	2 yrs.	IIb	140	76	85/77	7	..	..	Tincture	5 3	O.	1 day	-16	+5/7	-1	..	0	Cramps persisted 2 days after discontinuing.	0
24	Art.scler. heart dis.	Irreg. but long dur.	5 yrs.	III	154	76	135/71	14	1	1	Tincture	1.5 daily	O.	37 days	-14	-40/7	0	1, 3	0	Cramps and diarrhea 37th day.	0
25	Art.scler. heart dis.	Irreg.	2 mos.	III	187	56	155/76	16	2	1, 2	Tincture	6	O.	3 days	+8	+11	0	..	0	Nausea, vomit., but had occur'd before.	0
26	Art.scler. heart dis.	None	1 yr.	III	200	124	174/72	20	..	..	Solution	40	O.	5 days	-48	+2/7	-8	1	+	Slight anorexia on 6th day; quest. nausea.	0
27	Rheu. heart dis.	Irregular 1 yr.	1 yr.	IIb	142	80	130/60	0.18	1, 2	1, 2	Solution	1.5 daily	O.	16 days	-16	-8S -12D	-	3	0	0	0
28a	Thyrot. heart dis.	Infusion	3 yrs.	IIb	118	72	170/72	..	..	..	Solution	1.5 daily	O.	3 days	-10	..	..	..	0	0	0
28b	Thyrot. heart dis.	Infusion	3 yrs.	IIb	...	84	150/72	..	..	..	Tincture	20	O.	4 days	-8	..	..	..	..	0	0
29	Rheu. heart dis.	Maintenance	0 yrs.	III	140	92	124/76	16	1, 2	1, 2	Solution	20	O.	3 days	-32	-4/7	-10	+	0	Abd. discomfort 3d day; nausea and diarrhea.	0
30	Rheu. heart dis.	Irreg.	20 mos.	IIb	239	72	140/72	12	3	1, 2	Solution then tincture	2 daily	O.	5 days	-4	-15/7	-6	+	0	0	0

Conv.: Increase, +; decrease, -; no change, 0; elevated,  $\Delta$ ; depressed or inverted,  $\nabla$ ; diaphasic,  $\Delta\nabla$ ; flat, =; single dose, ; Rt., route; I.V., intravenous; O., oral.

The changes in blood pressure in the whole group were not decisive. Decreases were observed in 11 instances and increases in 7. As anticipated, a fall in venous pressure was found in 12 of 17 recorded readings.

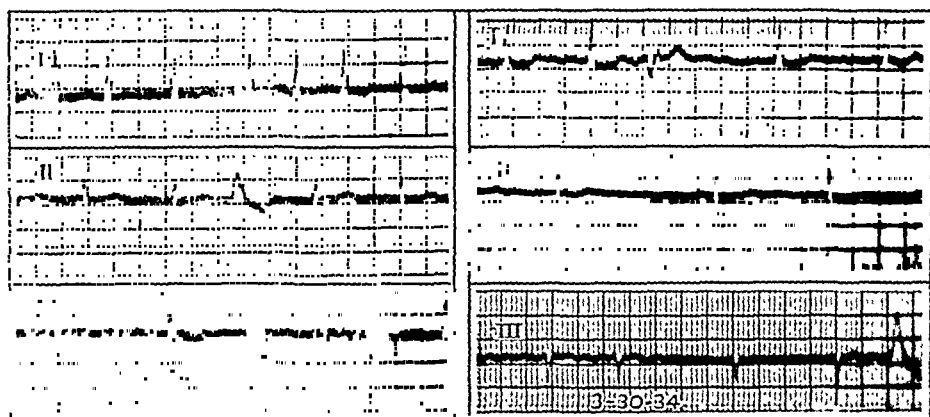


FIG. 3.—Electrocardiograms of Case 26, demonstrating the response to the oral administration of alcoholic solution of thevetin.

The electrocardiographic observations were especially illuminating. Demonstrable changes were observed in 19 instances. Lengthening of the auriculoventricular conduction time was noted 7 times; in 1 patient it was slightly shortened. If the cases of auricular

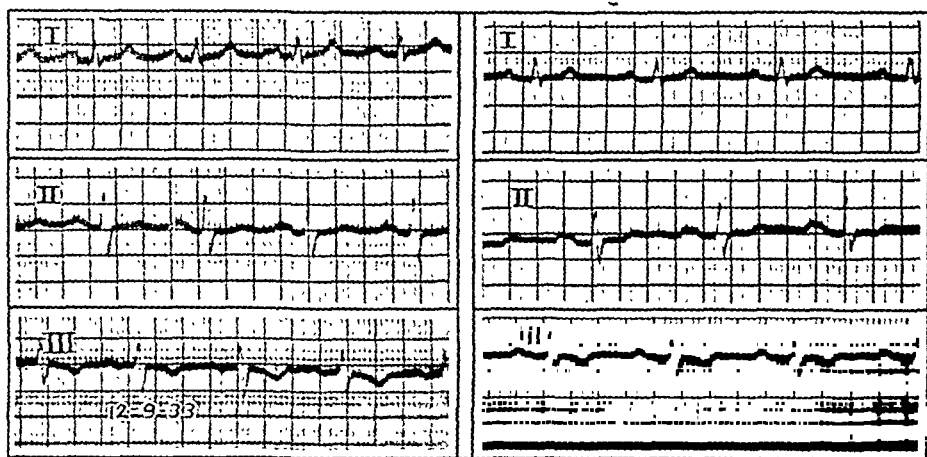


FIG. 4.—Electrocardiograms of Case 16, demonstrating prolongation of the *P-R* interval in response to the intravenous administration of thevetin.

fibrillation, 8 in number, be excluded from the group of 17 where a recheck was available, only 2 instances are left in which vagal stimulation was not manifest by an increased *P-R* interval after drugs of this series. In Case 16, the *P-R* interval was lengthened

from 0.2 to 0.25 second (Fig. 4). The electrocardiograms of 9 patients underwent changes in the  $T$  waves; in 5 of these, all  $T$  waves became negative. Deviation of the  $S$ - $T$  segments occurred in 9 instances and significant coving appeared in 3 (2 included in the 9 with  $S$ - $T$  deviation). Alterations in the  $Q$ - $R$ - $S$  complexes appeared in the electrocardiograms of 11 patients in this group. These changes included modifications of the time factors as well as the form of the  $Q$ - $R$ - $S$  waves. Five patients showed more frequent extrasystoles (Cases 12, 18 and 22) or extrasystoles only after these drugs (Cases 17 and 20). Case 9 showed an abolition of extrasystoles and Case 11 a few dropped beats after thevetin.

The control of decompensation was marked in 9 patients. In 6 water-logged subjects, diuresis resulted early and was a conspicuous feature in the movement toward restored circulatory balance. Dyspnea was relieved in 10 individuals. In 4 instances it was noted that these drugs were capable of maintaining circulatory equilibrium when utilized in place of digitalis at maintenance levels.

*Adverse Reactions to the Various Preparations of Be-still Nuts in Cardiac Decompensation.* The untoward effects recorded may be grouped under two headings, viz., disturbances of conduction and gastro-intestinal disorders. The simple extrasystolic arrhythmias so common as toxic manifestations to drugs of digitalis-like action may be dismissed without further comment; but the conduction changes in Case 13 were so unusual and bizarre as to deserve special comment. A hypertensive nephritic with myocardial degeneration and pronounced congestive failure had presented only bundle-branch block and occasional extrasystoles prior to the institution of the thevetin therapy. Fifteen cat units had been administered intravenously over a period of 47 hours, when coincident with a slowing of the pulse from 130 to 78 beats per minute, there appeared to auscultation a peculiar alteration of cardiac action. The electrocardiogram (Fig. 5) was revealing. There had apparently occurred a change in the pacemaker with an institution of nodal rhythm, and each regular  $Q$ - $R$ - $S$  complex was succeeded by an extrasystole. The bundle-branch block persisted and there was some debate as to the possible existence of an alternating bundle-branch block. The patient showed no subjective nor objective handicap and sinus rhythm was resumed 6 days after the discontinuance of thevetin.

In Case 18, death succeeded the third intravenous injection of 5 cat units of thevetin. The patient suffering from rheumatic heart disease with auricular fibrillation, showed a sharp fall in the radial pulse rate subsequent to the second intravenous dose of thevetin on the first day. Following the prescribed plan of electrocardiographic control of this intravenous medication, a third dose was administered on the second day (the ventricular rate having

risen from 72 to 75 to 80). Within a few moments the patient died. Necropsy permission was denied and the true explanation of this death must remain unrevealed. The only suggestion of an altered myocardial irritability lay in the more frequent extrasystoles which appeared in the electrocardiogram taken less than one-half hour before death. In no other detail was there a change from the preceding tracings except for the described slightly increased ventricular discharge.

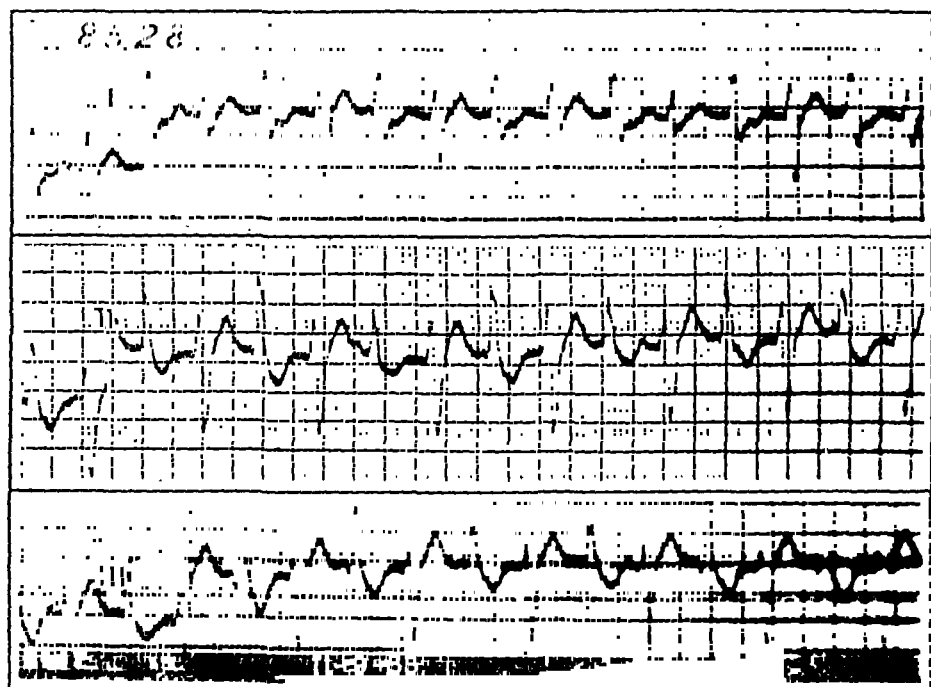


FIG. 5.—Electrocardiogram of Case 13 after 15 cat units of thevetin.

The patients receiving thevetin intravenously were remarkably free from gastro-intestinal symptoms of intoxication; anorexia, abdominal discomfort or cramps and diarrhea, singly or collectively, occurred in only 3 patients (Cases 15, 20 and 21). In 2 of these (Cases 15 and 20), the gastro-intestinal unrest subsided in spite of the continuance of the drug. The case for tincture of Thevetia and the alcoholic solution of thevetin by mouth was not as clearly cut. The first 2 patients receiving the tincture (Cases 22 and 23) suffered from cramps or diarrhea, nausea and vomiting on the 4th or 5th day. The 3d one taking the tincture (Case 24) had cramps and diarrhea on the 37th day. The 4th (Case 25) had a continuance of nausea and vomiting. Two other patients receiving maintenance dosage of the galenical preparation (Cases 28 and 30) were able to continue without discomfort. Likewise these same 2 patients had taken the alcoholic solution of thevetin for 3 and

5 days, respectively, with no inconvenience. Another patient (Case 26) was carried to theoretic tolerance and satisfactory therapeutic effect on the alcoholic solution of thevetin, with a slight sense of nausea on the last day. A 4th (Case 27) experienced no discomfort on effective maintenance levels of this form of thevetin; but a 5th (Case 29) had abdominal discomfort on the 3d day and nausea and vomiting thereafter.

Apparently, then, tincture of Thevetia possesses additional ingredients which are irritable to the gastro-intestinal tract. This seems enough to preclude its clinical use. The objections to the alcoholic solution of thevetin are less clearly defined and a much larger series of observations is required to answer this question. It is entirely possible that both may be found wanting just as were squill, apocynum and convallaria by White and his associates.<sup>15,16</sup>

**Summary and Conclusions.** Thevetin, a cardiac glucosid, has been isolated from the be-still nuts and its physical, chemical and pharmacologic properties established. Of particular promise is its digitalis-like action. By biologic assay its potency has been fixed as  $\frac{1}{7}$  that of ouabain. It is likewise  $\frac{1}{7}$  as toxic. Its action is more prompt and less sustained than digitalis. These facts serve as guides to its possible clinical applications and limitations.

The clinical trial of thevetin and other preparations of the be-still nuts in a group of 23 patients suffering from cardiac decompensation has justified certain deductions:

1. Thevetin and other preparations of the be-still nuts slow the heart rate in the presence of the normal conduction mechanism or of auricular fibrillation. In a single case of auricular paroxysmal tachycardia, no reduction of the cardiac rate attended the use of thevetin.

2. Electrocardiographic studies of patients receiving these preparations closely parallel the results of digitalis therapy. Lengthening of the *P-R* interval, inversion of the *T* wave, deviations of the *S-T* segments and alterations in the *Q-R-S* complexes are characteristic.

3. Compensation is restored and maintained in appropriate cases of congestive heart failure. Diuresis occurs in the course of this altered circulatory balance.

4. In the clinical use of thevetin more or less serious conduction faults may develop occasionally, even though every reasonable precaution has been exercised. This hazard may be minimized, if the potency and the comparative strength of this glucosid be borne in mind when it is used alone or in combination with drugs of similar action.

5. The irritant qualities of thevetin apparently deny its availability for intramuscular use.

6. The intravenous administration of thevetin has not been attended by evidence of local irritation or thrombosis.

7. Thevetin affords an added reliable and potent cardiac glucosid for intravenous use.

8. Extended study is necessary to determine the value of pure thevetin for oral use. The galenical preparations of defatted kernels, such as the tincture and the powder, appear to be clinically unsuitable because they frequently cause gastro-intestinal disturbances such as cramps and diarrhea.

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## QUINIDIN AND STRYCHNIN IN THE TREATMENT OF PREMATURE CONTRACTIONS.\*

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ONE of the most unsatisfactory complaints with which the physician must deal from the standpoint of therapeutics is extrasystolic arrhythmia. While most of these cases are not of serious moment, in some the extrasystoles may recur so frequently that the resulting pulse deficit causes symptoms that demand treatment. A pro-

\* Preliminary report was given before the Chicago Society of Internal Medicine, March 27, 1933.

longed search has therefore been made for means of affording relief to these sufferers.

Quinin has been used for many years by physicians on account of its supposed sedative action on the heart. Oppolzer,<sup>1</sup> the Viennese clinician, states, "The best and most powerful factors in dealing with heart patients are three: rest, digitalis, and quinine." Ludwig Traube<sup>2</sup> added quinin to digitalis to prevent or to relieve the disagreeable action of digitalis on the stomach. Many other clinicians observed that by using digitalis with quinin they could give larger doses without getting disagreeable symptoms.

Although clinicians, for the most part,\* seem to have forgotten about quinin, due to the lack of proper indications for its use, and also because it was shown experimentally by Santesson<sup>3</sup> and by Stokvis,<sup>4</sup> to have a paralyzing effect on the heart muscle, it was recalled to Wenckebach's attention in 1912 by a Dutch merchant, who used it to control his paroxysmal attacks of auricular fibrillation. Wenckebach,<sup>6</sup> in 1914, was apparently the first to record its deliberate use in the treatment of auricular fibrillation. He exploited the use of the very quality which had caused the older clinicians to abandon the drug. The effects of quinin in fibrillation were disappointing; however, the depressing, paralyzing action of the drug had a very favorable effect on the hyperactivity of the heart. He decided to try this form of treatment in other arrhythmias due to hyperkinesis.

It is well known that until this time there was no generally satisfactory drug or method of treating the most common of arrhythmias. Wenckebach,<sup>7</sup> in searching for specific drugs against extrasystoles, found that strychnin was often of value. However, strychnin, independently and alone, at times, was found to be absolutely ineffective. He then tried a combination of quinin and strychnin, writing in 1923,<sup>8</sup> "My experience with this treatment since the year 1915 has been so favorable that I am convinced that whoever will try it will come to the same conclusion."

Stimulated by these observations, Frey,<sup>10</sup> in 1918, studied the clinical pharmacology of the various cinchona derivatives in patients with auricular fibrillation. He found quinidin to be much more powerful than quinin; the difference appearing to be merely quantitative. Finding quinidin to be the most effective therapeutic agent, he recommended that the drug in the form of its more soluble sulphate be used clinically.

The drug's pharmacologic actions on the heart, so far as they are at present understood,<sup>11, 12</sup> are as follows:<sup>13</sup> (1) Mild inhibition of the vagus; (2) lowered rate of sinus impulse discharge; (3) slight decrease in *A-V* conduction; (4) lengthening of the refractory period of cardiac muscle and slowed conduction therein; (5) lessened ex-

\* H. Hochhaus<sup>5</sup> in 1907 recommended quinin combined with digitalis or camphor in the treatment of extrasystoles.



citability of the cardiac muscle;<sup>14, 15, 16</sup> (6) dilatation of the coronary arteries.\*<sup>21</sup>

Digitalis in toxic doses brings the heart to a standstill in systole; quinidin in diastole. In smaller doses, it leads to a definite depression of the strength of the heart beat. The principal effect of quinidin lasts for only 1 or 2 days. Wiechmann<sup>17</sup> states that excretion, principally in the urine, begins promptly and is greatest during the first 24 hours.

Strychnin, in therapeutic doses, according to Sollmann<sup>18</sup> is without effect upon the cardiovascular system. Kikuchi,<sup>19</sup> however, reports that strychnin produces a marked increase in the absolute strength of the frog's heart. This is in accord with the therapeutic results repeatedly observed by clinicians who have given the drug empirically as a cardiovascular tonic in spite of contrary opinions from experimental work on anesthetized animals.

White, Marvin and Burwell<sup>20</sup> incidentally mention the use of quinidin in 1 case of premature ventricular contractions which was materially aided. Boden and Neukirch<sup>21</sup> report success in the treatment of extrasystoles. Smith<sup>22</sup> (1921) states: "Drugs do not seem to influence their prevalence," and Rogers,<sup>23</sup> shortly afterward, writes: "I know of no drug which will directly improve this cardiac condition." The following year Smith<sup>24</sup> reports the use of quinidin in 20 patients with premature contractions. In 10 patients the irregularity was eliminated, while in 7 their frequency was diminished. Singer and Winterberg<sup>25</sup> report favorably, whereas Viko, Marvin and White,<sup>26</sup> in 1923, state: "The data at present available are inconclusive regarding the value of quinidine in treating cases with premature beats." Kerr and Bruck<sup>27</sup> report several cases of extrasystoles successfully treated with quinidin. Musser,<sup>28</sup> in treating a considerable series, had very good results in 60% of his cases without noting bad results from its use. Barrier<sup>29</sup> was able to abolish them in more than 90% of cases. Bishop<sup>30</sup> feels that it is of distinct clinical value, and Maynard<sup>31</sup> advises its use in the treatment of these patients. McGuire's<sup>32</sup> experience with 50 cases of extrasystoles was favorable; if success occurred it was usually noted within the first 24 hours. Lewis<sup>33</sup> states: "The only drug that frequently stops extrasystoles is quinidine given in doses of 2 to 5 grains twice or thrice daily." He warns that, "Digitalis should not be used."

Other observers have not obtained such good results. Wolferth<sup>34</sup> believes that quinidin has a very limited field of usefulness in the extrasystolic arrhythmias. Otto and Gold<sup>35</sup> state: "The results of our studies indicate that both of these drugs (quinin and quinidin) have a limited field of usefulness in the treatment of patients with premature contractions and, furthermore, that digitalis deserves a

\* Quinin dilates bloodvessels in general and lowers the blood pressure.<sup>25</sup> Presumably quinidin has the same effect.

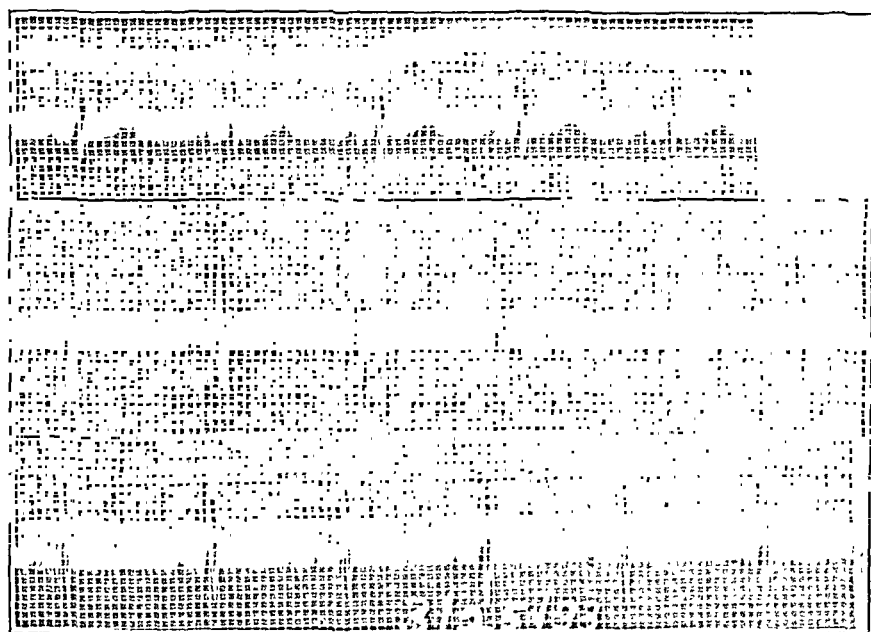
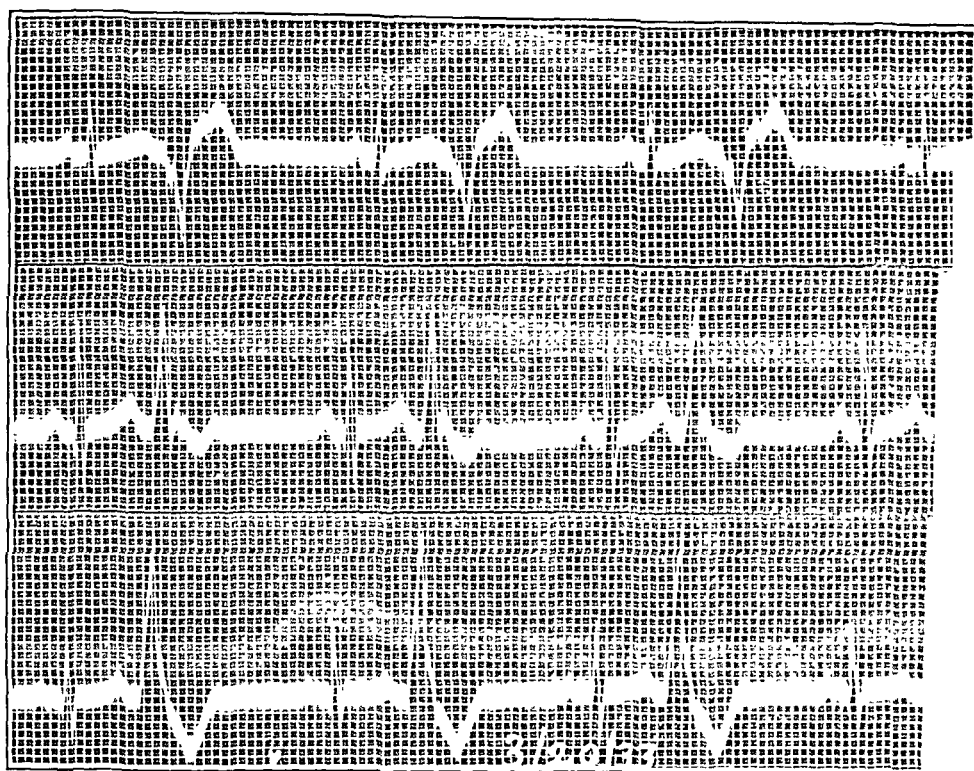
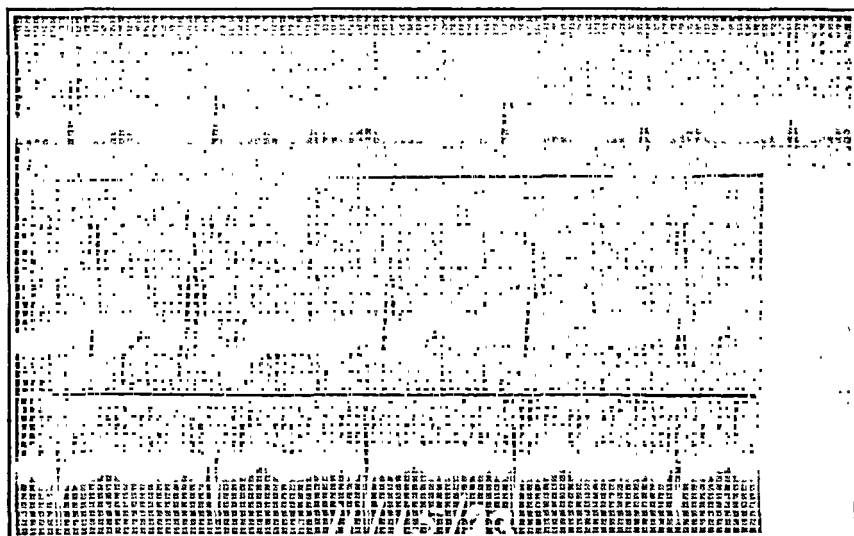


FIG. 1.—Electrocardiograms of Case 2. *A* is the record before medication; *B* is the record after medication.

A



B

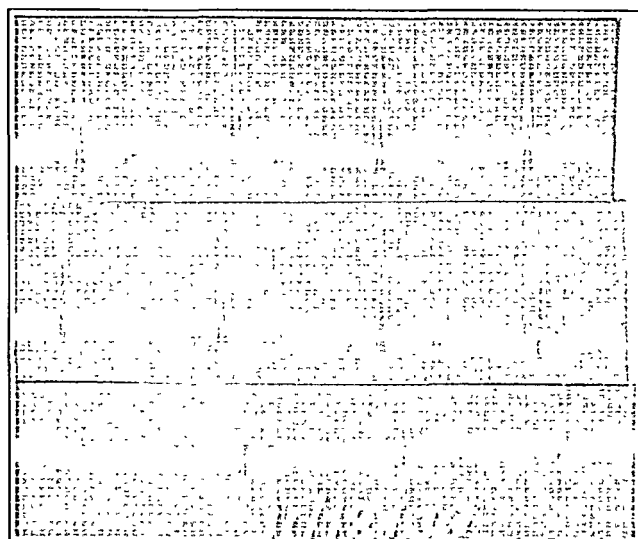


FIG. 2.—Electrocardiograms of Case 3. *A* is the record before medication; *B* is the record after medication.

more prominent place in the treatment of the premature contraction than it has heretofore received." Korn<sup>36</sup> reports a case of paroxysmal tachycardia in which the dose of quinidin required to control the associated extrasystoles was too high to be practicable.

No further reports on the combined use of quinidin and strychnin have been found in the literature.

**Case Abstract.** A laborer, aged 60, was first seen on August 15, 1931. He had had 6 attacks of syncope during the preceding 3 years. The last attack, 1 month previously, occurred after an hour's walk. It was longer and more severe than usual. These attacks lasted from 15 to 30 minutes following exertion such as walking, but had occurred while the patient was quietly resting. He usually felt the attack coming on, when everything around him would "start swimming around." As a rule he did not completely lose consciousness, although he was unable to move because of faintness. Once he fell, injuring his head. Palpitation, following exertion and also while lying quietly in bed, had been noticed during the previous 3 years. Weakness and dyspnea on climbing stairs and dull, aching pains in the calves of the legs had been present for 2 months. These were as severe in bed as when walking and had frequently kept him awake for 3 or 4 hours at night. Weakness had been more marked since his last attack of syncope. The patient felt that he was becoming progressively worse. There were no other complaints. He had had scarlet fever at 21, typhoid fever at 37, influenza at 49, and again at 56 years. There was no history of rheumatism, sore throat, diphtheria or pneumonia.

The pupils reacted to light and in accommodation. The left pupil was slightly notched. The cervical veins were engorged. The chest was fixed in inspiration. The lungs were slightly hyperresonant with transient subcrepitant râles in both bases posteriorly. There was a palpable impulse in the suprasternal notch. The point of maximum impulse of the apex beat was not visible or palpable. The lower sternum was resonant. The left heart border was 1 cm. outside the midclavicular line in the 5th interspace. The right border was at the right edge of the sternum. There were no murmurs; no thrill. The aortic second sound was ringing. The impulse at the apex was 64, at the wrist 28 per minute. The rhythm was irregular, almost every alternate beat being an extrasystole. Radial and carotid vessels were moderately thickened. Blood pressure taken at a later date was 140/90. All deep reflexes were brisk. There were no other significant clinical findings. Wassermann and urine examinations were negative. The diagnosis was arteriosclerotic heart disease, cardiac enlargement, ventricular premature contractions, type 2b.

On August 15, 1931, an electrocardiogram was taken. On August 22, 1931, the patient was given strychnin sulphate, gr.  $\frac{3}{16}$ , 3 times daily for 1 week. He felt improved but was still weak with many extrasystoles and a pulse deficit of 48; the apical pulse being 80, the radial pulse 32 per minute. The strychnin was continued, and in addition he was given quinidin sulphate, gr. iii, twice daily, for another week. On September 5, 1931, he was definitely improved, the rhythm was regular and there was no pulse deficit; the pulse being 40 at apex and wrist. Continuing the quinidin and strychnin for a month, the rhythm was found to be regular with a pulse of 64 at wrist and apex. Another electrocardiogram at this time revealed absence of extrasystoles, but left axis deviation and myocardial damage were still evident.

The strychnin was stopped, but the quinidin (gr. iii, 3 times daily) was continued for 2 weeks. By this time, October 17, 1931, the patient was having considerable shortness of breath, palpitation, and several extra-

systoles were noted. He was advised to take both quinidin and strychnin; felt much better within 2 or 3 days and, 1 week later, October 24, 1931, the

TABLE 1.—ANALYSIS OF DATA. CASE 1.

Date.	Complaint.	Findings.	Treatment.	Remarks.
1931:				
8/15	S; W; P; D	Left heart enlarg.; freq. XS	Ekg. ordered; no medication	Ret. 1 wk.
8/22	W; D; P	Freq. XS; pulse at apex 64, wrist 28	S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/29	Impr. but weak	Freq. XS; pulse at apex 80, wrist 32	Q. gr. iii b.i.d.; S. gr. 1/60 t.i.d.	Ret. 1 wk.
9/5	Improved	Rhythm reg.; pulse 40	"	Ret. 2 wks.
9/19	About the same	Rhythm reg.	"	Ret. 2 wks.
10/3	Still weak	Rhythm reg.; pulse 64	Stop S. cont. Q.	Ret. 2 wks.
10/17	D; P on exert.; feels cold	Several XS; pulse 72	Q. cont.; start S. gr. 1/60 t.i.d.	Ret. 1 wk.
10/24	Feels much better	Rhythm reg.; pulse 68	Q. cont.; start S. gr. 1/60 t.i.d.	Ret. 2 wks.
11/7	Feels "pretty good;" P and D occas.	No arrhythmia; pulse 60	Stopped RX. for 7 days	Ret. 2 wks.
11/14	Relapse; D and W marked	Freq. XS	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Not seen
11/21	Improved	XS present	"	Ret. 1 wk.
11/28	Feels much better	XS still present	"	Ret. 2 wks.
12/12	Feels OK	Pulse 60; reg.	"	"
12/26	Feels better	No XS; pulse 60	"	"
1932:				
1/9	No Q and S. for 3 days; felt bad; began Q. and S.; feels OK	XS present; pulse deficit	"	"
1/23	Feels OK	Few XS; pulse 60	"	"
2/9	"	"	"	"
2/20	"	"	"	"
3/5	"	Pulse: apex 60, rad. 48	"	"
3/19	"	Pulse: apex 72, rad. 60	"	"
4/2	Slight D	Pulse 48; freq. XS	"	"
4/4	Slight D	"	K. I. m. x t.i.d.	Ret. 5 days
4/9	Slight D	"	"	Ret. 2 wks.
4/23	Precordial pain; mild D; pain in legs	"	"	Ret. 3 wks.
5/7	Feels fine	Heart reg.	"	Ret. 1 mo.
5/21	Feels fine	Heart reg.	"	Ret. 1 mo.
6/8	OK except on hot days; pains in legs severe	Occasional XS; iodid rash	"	Ret. 1 mo.
7/16	D on exert.; no P	No XS	K. I. m. v t.i.d.	Ret. 2 wks.
7/30	D on exert.; no P	No XS	Add Dig. m. v t.i.d.	Ret. 1 wk.
8/6	Not feeling so well	XS q. 8 to 10th beat	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/13	Feels much better	XS about q. 60 beats	Q. gr. ii daily; S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/20	Feels better	XS q. 15 to 30 beats	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/27	Felt bad q. alt. day	XS q. 15 to 30 beats	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Ret. 2 wks.
9/10	Feels very well	XS q. 120 beats	Q. gr. ii daily; S. gr. 1/30 alt. b.i.d. and t.i.d.	Ret. 2 wks.
9/18	Tinnitus; face flushed	Not seen	Q stopped; S cont.	Not seen
9/24	Feels OK	XS q. 120 beats	Q. gr. i q. alt. day; S. gr. 1/30 alt. b.i.d. and t.i.d.	Ret. 2 wks.
10/8	Had a cold; many XS	XS q. 40 beats	"	Ret. 2 wks.
10/21	Feels OK	Still has XS	"	Ret. 2 wks.
11/2	Tinnitus; face red and hot	Not seen	No Q. and S. for 2 days	Felt OK
11/4	Asks for adequate Q. and S.	No XS; pulse 80	Q. gr. ii daily; S. gr. 1/30 b.i.d.	Ret. 2 wks.
11/18	Feels fairly well	Pulse 76, reg.	"	"
12/2	Better than in months; walked 2 mi.; felt OK	Rhythm reg.	Q. gr. ii q. A.M. S. gr. 1/30 q. P.M.	"
12/16	No XS for 6 wks.; Pt. OK	Rhythm reg.	"	"
1933:				
3/15	No complaints	No XS at any time	"	Ret. q. 2 wks.
10/18	No complaints	Rare XS detected	Q. and S. stopped	Ret. q. 2 wks.
12/9	No complaints	Rare XS detected	No medication	Ret. q. mo.

S = syncope. W = weakness. P = palpitation. D = dyspnea. XS = extrasystoles.

rhythm was again regular, at a rate of 68. After being free of extrasystoles for 2 weeks he was advised, on November 7, 1931, to stop both the quinidin and strychnin for 7 days. He became tired, extrasystoles developed, and he finally became so shaky, weak, and short of breath that he "could not walk across the room without puffing." Strychnin and quinidin gave symptomatic relief within a week, although extrasystoles persisted during the following 3 weeks. The pulse then remained regular for about a month. On January 3, 1932, he again tried to stop the quinidin and strychnin for 3 days, felt worse, started both drugs again, and soon felt much better. However, extrasystoles along with a pulse deficit, persisted during the following 3 months. On April 4, 1932, the strychnin and quinidin were stopped and the patient was given a saturated solution of potassium iodid (10 min. 3 times daily). He was symptomatically improved but the extrasystoles, although decreased in frequency, persisted for a month. From May 7, 1932, to July 30, 1932, the rhythm remained

TABLE 2.—SUMMARY OF ADDITIONAL CASE HISTORIES.

No.	Sex.	Age.	Symptoms— Findings or diagnosis.	Previous treatment.	Results of Q and S.	Remarks.
2	M	10	Severe headaches; dysp.; prec. pain	Br and KI, 5 mos.; no relief	Reg. rhythm for 3 wks.	Rheum. and XS recurred for 6 wks.; no Q and S and no XS 14 mos.
3	F	38	Dizziness; B.P. 240/ 150; marked dysp.; smothering attacks	Br, KI, MgSO <sub>4</sub> for 3 mos.; no relief	Reg. rhythm; pt. greatly improved	No Q and S, 2 wks.; XS recurred; Q and S again controlled XS; pt. followed for 2 mos.
4	M	55	XS q. 3 to 5 beats; exam. 14 x during 9 mos.	Br, QS, D, and Qx; no relief	Reg. rhythm for 1 mo.	Heart reg. when last seen 5 mos. later.
5	M	63	Angina; freq. XS; dysp.; EKG. showed cor. occl.	D and KI, 2 wks.; XS per- sisted; no re- lief	Reg. rhythm; def. relief for 3 wks.	During and after removal of 12 teeth, Q and S—no relief—and failed to control the XS.
6	M	74	Occas. precor. pain, palp.; felt stoppage of heart	D for 3 wks.; XS persisted; no relief	Reg. rhythm; compl. relief for 1 wk.	Later, during chest cold for 1 mo., Q and S gave no relief and XS persisted.
7	F	60	Dysp. and sl. edema of feet; XS q. 3 to 4 beats	D for 15 mos.; no relief; Qx reduced XS	Reg. rhythm; marked relief	Observed since 4/1/32; Q and S first given on 11/29/33; Q and S still gives relief.
8	M	73	Epileptic attacks; bi- geminy-rate 80	Unknown	Reg. rhythm for 6 mos.	Reducing Q and S caused XS to recur q. 3 to 6 beats.
9	F	60	Dysp., dizzy; fullness in chest and XS for 2 yrs.	D for 6 wks.; part. relief; XS remained	Rare XS only during 1 yr.; def. relief	More active later; overfatigue then caused XS to recur even with Q and S.
10	M	65	Early heart failure; freq. XS; arterioscl.	KI for 2 wks.; no relief	Reg. rhythm; relief 3 mos.	No Q and S, 2 wks.; XS q. 4 to 5 beats, Q and S again con- trolled the XS.
11	F	30	Occas. attacks XS; parox. tachy.	Qx repeated; no relief	Q and S 3 dys.; relief	No attacks, 6 mos.; rare since; controlled by routine Q and S.
12	F	39	Mitr. sten.; D intox. freq. XS	No D, 2 mos.; XS persisted	Reg. rhythm; relief	Overfatigue caused XS, even with Q and S.
13	F	65	Edema def.; dysp.; XS; q. alt. beat	D and Bed, 6 wks.; no relief	XS less freq.; def. relief	Periodically for 18 mos.; Q and S decreased XS; relief.
14	M	69	HBp; palp.; XS mis- taken fib.	No. col. or tob.; no relief	Relief 3 dys.; cont. 3 wks.	No Q and S, 3 mos.; reg. rhythm; mental strain=XS; relief by Q and S.
15	F	17	Early heart failure; mitral sten.	D and KI; no relief	XS dec. freq.; def. relief	A rheum. heart with marked myocardial damage.
16	F	54	Pit. obesity; dysp.; freq. XS	D and Qx; no relief	XS persists; no relief	Q and S to toxicity; no relief; thyroid med. also failed.
17	M	62	Early heart failure	Unknown	XS dec. freq.	Def. impr. observed, 2 wks.
18	F	46	BMR—48; freq. XS	Unknown	No effect	Thyroxin cured myxedema.
19	F	18	Palp. precor. pain; rheum. ht.; freq. XS	QD; bed rest; no imp. 1 mo.	Reg. rhythm; def. relief	Tonsils out; no XS, 3 mos.; XS recurred; relief by Q and S.
20	M	63	Dyspnea; freq. XS	D; no effect	Reg. rhythm	Def. sympt. improvement.
21	M	63	Prec. pain; dizziness; puls. bigem.	Q, 2 dys.; no relief	Reg. rhythm; def. relief	No Q and S after 2 wks.; had XS from D; XS stopped by Q and S.

Br = sodium bromid.

BMR = basal metabolic rate.

Dig. (Table 1) or D (Table 2) = Tr. digitalis.

EKG. = Electrocardiogram.

HBp = Arterial hypertension.

KI = Sat. sol. of potassium iodid.

q. = every.

x = times.

Q = quinidin (Table 1) and quinin sulph. (Table 2).

Qx = Quinidin sulphate (Table 2).

QD = Quinidin dihydrobromid.

Q and S = Quinidin and strychnin.

Rx = Treatment.

XS = Extrasystoles.

regular. Tincture of digitalis (5 min. 3 times daily) was then added to a 5 min. dose of the ioidid. The patient did not feel so well and, a week later (August 6, 1932), extrasystoles every eighth or tenth beat were found. Both the ioidid and digitalis were stopped and he was again given quinidin (gr. iii daily) and strychnin (gr.  $\frac{1}{60}$  3 times daily). Although the patient felt improved and extrasystoles were less frequent with this medication, they were repeatedly noted during the following 3 months. On November 4, 1932, the patient stated that he had "gotten nowhere" during the previous 6 months. He asked to be put back on an adequate dosage of quinidin and strychnin. His request was granted. He felt well and only rarely were extrasystoles noticed on biweekly examination during the following 11 months. On October 18, 1933, the quinidin and strychnin were stopped and on repeated examinations to January 26, 1934, only a rare extrasystole was found. At this time he stated that he was short of breath and felt as "he did before." From February 2, 1934, to March 9, 1934, strychnin sulphate, gr.  $\frac{1}{30}$  t.i.d., with sodium bromid, gr. xv t.i.d., failed to give relief. On March 9, 1934, he was put on routine quinidin and strychnin management. He has felt well and no extrasystoles have been noted on repeated examinations to December 15, 1934.

Twenty other patients were given quinidin and strychnin; 8 were private patients and 12 selected from a series of 53 dispensary cases of extrasystoles. The arrhythmia was marked and persistent in each case. All had mild to moderately severe symptoms and signs due entirely or partially to extrasystoles. Most of them had previously tried various drugs without obtaining relief from the arrhythmia. Quinidin sulphate (gr. iii) and strychnin sulphate (gr.  $\frac{1}{30}$ ) thrice daily were routinely administered. Treatment was entirely successful in 16 of these cases. Two cases, 16 and 18, were complete failures. In Case 16 quinidin sulphate (gr. x) and strychnin sulphate (gr.  $\frac{1}{30}$ ) thrice daily, for 5 days, were finally given without the extrasystoles being decreased in frequency. One patient, Case 6, obtained complete relief at first, but failed to return regularly after recovery from his chest cold. One patient, Case 15, was symptomatically relieved and had fewer extrasystoles after medication although the arrhythmia persisted.

The relatively little interest that has been shown in the treatment of premature contractions is perhaps the result of the frequently quoted opinions of Mackenzie<sup>37</sup> and Lewis,<sup>38</sup> that extrasystoles are of little practical importance. Frequently the patient is reassured, the supposed prognostic insignificance of extrasystoles explained, and months or years are often allowed to elapse without relief being obtained.

Possibly the chief factor in preventing the more widespread use of quinidin is the number of warnings that have been given regarding the dangers of the drug. That these dangers have been overemphasized has been pointed out by many clinicians.<sup>26, 36, 39, 40, 41, 42, 43</sup> Barrier<sup>29</sup> mentions that induction of ventricular tachycardia and ventricular fibrillation are among the dangers of quinidin therapy, a possibility which others have considered.<sup>14, 44</sup> Levy<sup>45</sup> advises stop-

ping quinidin after the onset of a persistently high ventricular rate. That such stimulative effects are unlikely is evidenced by the experiences of several observers.<sup>14, 42, 46, 47</sup> White<sup>48</sup> has given an excellent summary of the dangers attendant on quinidin administration. He states: "Serious accidents can happen during quinidin therapy, but they are very rare and, in carefully selected cases, very unlikely." Large doses of quinidin do unduly depress the heart muscle. There is no reason to believe that in the small therapeutic dosage used here, it would have this effect. The mild depressing effect exhibited by such doses leads to a prolonged interval of rest for the heart muscle and is certainly less harmful than the secondary effects of the extrasystoles which the quinidin is used to combat. This recalls Wenckebach,<sup>49</sup> who said: "Our most useful and valuable drugs are poisons when given in sufficiently large doses."

In treating auricular fibrillation it was formerly the custom to produce a normal mechanism with quinidin, stop the quinidin and count those cases that return to fibrillation as failures. That this is wrong was pointed out by Barrier.<sup>29</sup> A similar course has frequently been followed in the treatment of extrasystoles. The quinidin and strychnin should not be stopped, but the minimal daily amount necessary for the continuation of a normal mechanism should be determined for each individual, and this dosage maintained, at least, over a considerable period. It is often important to give frequent small doses because of the rapid excretion of both drugs. Although obviously the most interesting effects of any drug are those observed in the treatment of the more severe disturbances, as the cases of extrasystoles here presented, quinidin and strychnin have proved helpful in controlling extrasystoles in otherwise normal as well as in diseased hearts. A tendency of the extrasystoles "to escape," thereby creating a demand for increasingly larger doses of quinidin, as noted by Otto and Gold,<sup>35</sup> has not been observed.

The advantages of the combined use of quinidin and strychnin in the control of the extrasystolic arrhythmias, as suggested by Wenckebach, seem to have been underemphasized. We can completely confirm Wenckebach's observations regarding the favorable effects of quinidin and strychnin treatment of certain patients with premature contractions.

**Summary.** A laborer, aged 60, with attacks of dizziness, palpitation, and syncope for 3 years, weakness, and dyspnea on exertion for 2 months, and findings of moderate arteriosclerosis, pulmonary emphysema, engorged cervical veins, slight left heart enlargement, and frequent ventricular extrasystoles, has been observed for over 40 months. With experimental precision strychnin sulphate and quinidin sulphate, were given separately, together, and discontinued. Potassium iodid alone and in combination with digitalis was tried instead of quinidin and strychnin. Together quinidin and strychnin gave the greatest freedom from extrasystoles and from



symptoms. Under these two drugs his compensation improved. Without them, with strychnin or quinidin separately, with iodid and especially with digitalis the extrasystoles increased in frequency and his condition was correspondingly worse.

Sixteen of 20 other patients with mild cardiac decompensation due to extrasystoles when similarly treated with a combination of quinidin and strychnin showed a favorable response.

NOTE.—We wish to thank Dr. Harry A. Richter for permission to include 2 cases which have been under his care.

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## CARDIOVASCULAR RESPONSE TO THE SUBCUTANEOUS INJECTION OF EPINEPHRIN AND PITUITRIN IN ESSENTIAL HYPERTENSION.

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THE cardiovascular response to the injection of epinephrin and pituitrin in normal persons has been adequately studied, but the response to such injections in essential hypertension where, aside from the question of endocrine imbalance, altered hemodynamics prevail, is worthy of study. It would be of interest to know whether a consistent qualitative or quantitative variance from the normal response obtains in this condition. We wish to report the results of such an investigation.

**Method.** The response was studied in 40 hospitalized patients with essential hypertension in whom the state of the arteries, the integrity of the cardiac and renal function and the lability of the blood pressure were known. Of these 25 were females who varied in age from 41 to 80, averaging 59.2. The 15 males were distributed between the ages of 34 and 80, with an average of 60. The systolic and diastolic blood pressure and the pulse rate were determined at 5-minute intervals for 60 min. in each of 32 of the above patients following the subcutaneous injection of 1 mg. (1 cc. of a 1 to 1000 solution) of epinephrin. The response to the injection of 1 cc. of obstetrical pituitrin (Parke, Davis & Co.) was studied in all of the 40 patients. Before giving the injection, the basal levels of the blood pressure and of the pulse were determined. The patient remained prone in bed throughout the observation period. All readings were made by a single observer. The pulse was counted for a full minute at each 5-minute interval.

The blood pressure was read on a mercury sphygmomanometer, and the change of sound was regarded as the diastolic pressure level. The site of injection was not massaged.

**The Epinephrin Response.** The subcutaneous injection of from 0.5 to 1 mg. of epinephrin in healthy individuals is followed inconstantly by a rise in systolic blood pressure, a fall in diastolic pressure with increase in pulse pressure, and a rise in pulse rate<sup>1</sup>. These changes may vary in intensity from a reaction which assumes alarming proportions to no response whatever, apparently dependent upon individual differences in the rate of absorption and upon the more ill-defined factor of threshold of sensitivity of the cardiovascular apparatus. The frequency with which the typical reaction occurs varies so greatly, according to the reported studies on normal persons, that a statement of its probable incidence cannot be made. In 35 patients with apparently minor functional ailments, Bauer<sup>2</sup> found that 7 did not show a pulse increase over 8 beats per minute, and 15 patients did not show an elevation in systolic pressure of as much as 10 mm. of Hg. Peabody *et al.*<sup>3</sup> studied the response in 27 normal men and in 65 soldiers with irritable hearts. A positive reaction, defined as a rise in systolic pressure or of pulse rate over 10 or 15 points together with subjective symptoms, was not encountered in the first group. In the soldiers with irritable hearts a positive reaction occurred in 60%. On the other hand, Jensen,<sup>4</sup> Schulten *et al.*,<sup>5</sup> Blumgart<sup>6</sup> and others have observed the occurrence of the typical response quite uniformly in normal individuals.

The normal variation being so wide, it is not surprising that observers are in disagreement as to the interpretation of the response in hypertension. One group, led by Kylin, believe that the response is inconspicuous in this condition, whereas others claim that there is a rise in blood pressure of unusual intensity following epinephrin injection. Jensen,<sup>4</sup> who has conducted the most careful investigation, found that his patients with hypertension fell into two clinically indistinguishable groups, depending upon their reaction to a first and to a second subcutaneous injection of epinephrin. The first group did not respond until they were given the second injection, after which an intense and prompt increase in systolic pressure occurred. The second group of patients responded in a similar manner, but to the first injection. He could not explain the lack of response to the first injection characterizing the first group. He concluded that the response exhibited by the hypertensive patients was significantly different from the slow rise and slower decrease in pressure found in normal persons.

In Chart I the average response of our patients, as observed over a period of 60 min., is represented graphically. The average systolic pressure falls slightly for a period of 35 min., after which it rises, to remain slightly above the initial level. The average diastolic pressure falls 8 mm. in 5 min., reaching a maximum decrease of

17 mm. at 45 min. At the conclusion of the observation period it is still 12 mm. below the initial level. These changes produce a pronounced increase in pulse pressure. The average pulse rate rises steadily to an increase of 13 beats per minute at the 60-minute period.

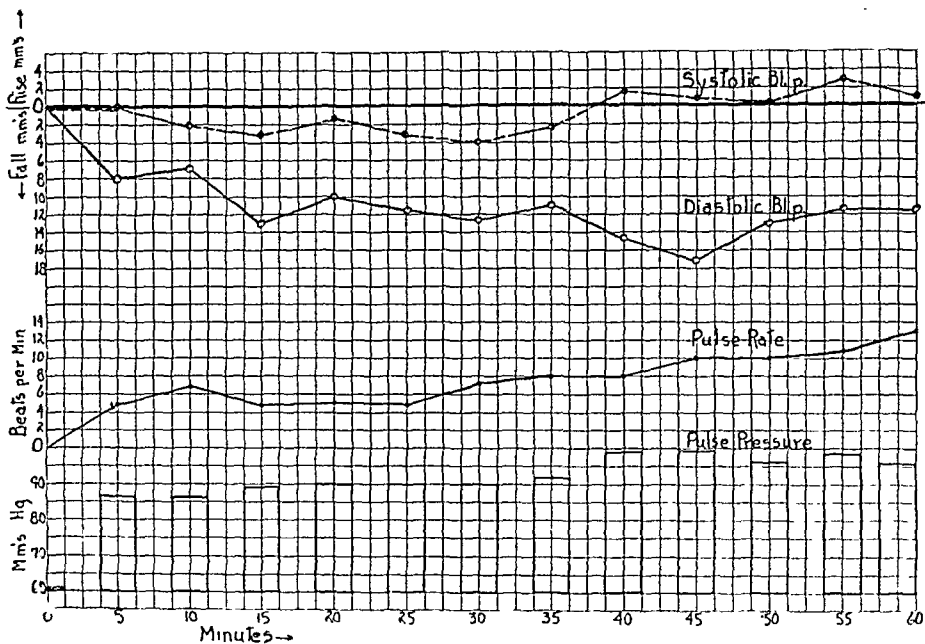


CHART I.—Average cardiovascular response to epinephrin of 32 persons with hypertension.

Analysis of the individual responses was not informative. A brisk pronounced increase (over 10 mm. of Hg in 20 min.) occurred in 5 patients only. There were no clinical characteristics to distinguish them from the remainder of the group. In general, the nature of the response was independent of previous lability of blood pressure, original height of blood pressure, size of heart, and presence of arteriosclerosis or detectable renal injury.

Pain in the left chest was experienced by 2 patients who clinically did not have angina pectoris but whose electrocardiograms gave evidence of myocardial damage. No other subjective sensations were complained of by any member of the group.

**Mechanism of the Epinephrin Response.** In Table 1 the changes encountered in the blood pressure are compared with the changes in pulse rate. Fall in diastolic pressure was an almost uniform finding and occurred independently of rise or fall in pulse. Fourteen patients showed a rise in systolic blood pressure of 10 mm. or more. In 12 of them, the pulse rose 5 beats per minute or more. In only 1 was there a fall in the pulse rate of similar magnitude. In 17 patients responding by a fall in systolic pressure, only 8 showed a

rise in pulse rate, while in 7 the pulse was unchanged, and in 2 the rate fell. Apparently there existed a degree of parallelism between the changes in systolic pressure and in pulse rate such that a rise in pressure was quite uniformly accompanied by a rise in pulse rate, whereas in over half of those patients showing a fall in systolic pressure, the pulse was either unchanged or likewise fell. These findings are in accord with the conception originally stated by Bauer,<sup>2</sup> that two mechanisms are involved in the epinephrin reaction, namely, arteriolar dilatation causing a fall in diastolic pressure, and stimulation of the heart causing a rise in systolic pressure. Furthermore, Schulten *et al.*<sup>5</sup> have recently shown that following the injection of epinephrin there is an initial increase in venous return to the right heart (which hardly accords with the conception of arteriolar constriction), followed by a rise in systolic pressure and pulse rate, a pooling of blood in the lungs, and eventually an increase in cardiac output. This perhaps indicates that the cardiac stimulation is both active, as the direct result of the epinephrin itself, and passive, in response to increase in venous pressure. The vigor of response could well be altered by decrease in cardiac reserve which commonly accompanies long-standing hypertension. We suggest this as the explanation for the minimal response, as regards systolic pressure and pulse rate, encountered in so many of our patients. With this possible reservation, we were unable to convince ourselves that the cardiovascular response of our hypertensive patients to subcutaneously injected epinephrin differed in any consistent respect from the normal.

TABLE 1.—RELATION OF CHANGE IN BLOOD PRESSURE TO CHANGE IN PULSE RATE FOLLOWING SUBCUTANEOUS INJECTION OF EPINEPHRIN.

	No. of cases.	Pulse rises over 5.	Pulse falls over 5.	Pulse unchanged.
Rise, sys. pressure, 10 mm. or more . . . . .	14	12	1	1
Fall, sys. pressure, 10 mm. or more . . . . .	17	8	2	7
No change, sys. pressure . . . . .	1	1	0	0
Rise, diast. pressure, 10 mm. or more . . . . .	2	0	1	1
Fall, diast. pressure, 10 mm. or more . . . . .	30	21	2	7
No change, diast. pressure . . . . .	0	0	0	0

**The Pituitrin Response.** The response of the normal cardiovascular system to the intramuscular injection of pituitrin has recently been studied in detail by Moffat.<sup>7</sup> Contrary to widespread impression and to results obtained in animal experimentation, he observed only slight changes in blood pressure and pulse rate of 62 individuals observed over a period of 60 min. following injection. In general, there was a slight fall in pressure, affecting primarily the systolic, and a consequent decrease in pulse pressure. The pulse rate was not appreciably altered. In 3 individuals with hypertension, a pronounced fall in systolic pressure was observed.

With the exception of these 3 instances, we have not encountered

any study dealing with the cardiovascular response to the injection of pituitrin in arterial hypertension.

The average response exhibited by our group of 40 patients is expressed in Chart II. Five minutes after injection, there is an average rise in systolic pressure of 6 mm., and in diastolic of 4 mm. At 20 min., the diastolic pressure has risen 5 mm., near which level it remains throughout the observation period. From 20 to 40 min. the average systolic pressure falls gradually over a distance of 6 mm. after which it returns slowly toward the preinjection level. The average pulse pressure is slightly lessened during the period of systolic fall. The average pulse rate remains unchanged.

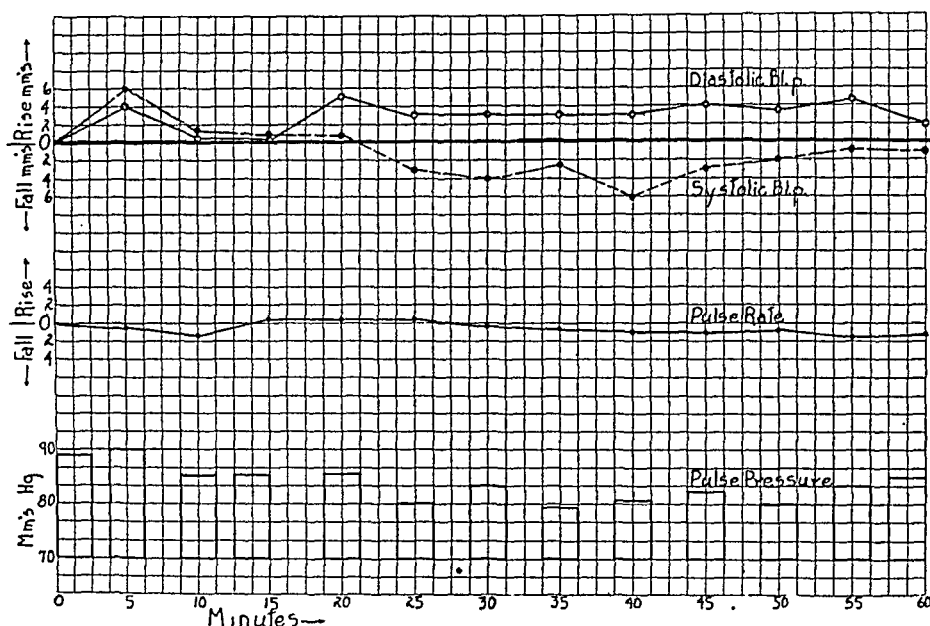


CHART II.—Average cardiovascular response to pituitrin of 40 persons with hypertension.

The individual changes exhibited by each patient were graphed in an effort to determine what effect the initial height of the blood pressure had upon the response. No consistent trend could be demonstrated. Those patients showing either a pronounced rise or fall were likewise studied to see if any clinical characteristic distinguished them as a group. None could be ascertained. The response of these same patients to epinephrin was likewise reëxamined wherever possible, to see if it differed by any consistent particular from that exhibited by the remainder of the group. These comparisons proved fruitless. We could not demonstrate that those patients showing a pronounced reaction to pituitrin injection were unduly vigorous or atypical in their epinephrin response.

It is evident that the cardiovascular response to pituitrin in our hypertensive series differed in no noteworthy respect from that obtained by Moffat in normal individuals. We are not even sure that the inconsequent fall in average systolic pressure and rise in average diastolic pressure observed in our series were due to pituitrin. It might be a chance reflection of the lability of blood pressure commonly encountered in hypertension patients when they are observed over a period of time. Since, however, Moffat obtained identical results in his patients, the conclusion is probably warranted that it was in fact a pituitrin effect.

**Summary.** 1. The blood pressure and pulse rate were measured at 5-minute intervals over a 60-minute period in 32 individuals with essential hypertension who had received a subcutaneous injection of 1 mg. of epinephrin.

2. The average systolic pressure fell slightly over a period of 35 min. and then returned to the preinjection level; the average diastolic pressure fell to a maximum low point at 45 min. and remained near that level throughout the remainder of the period. The average pulse pressure decreased. The average pulse rate rose.

3. A degree of parallelism existed between changes in the systolic pressure and in the pulse rate of these patients, such that a rise in pressure was usually accompanied by a rise in pulse rate, and a fall in systolic pressure by either a lowered or unchanged pulse. Elevation of systolic pressure may be primarily the result of cardiac stimulation by epinephrin, whereas the fall in diastolic pressure is attributable to arteriolar dilatation.

4. In 40 hypertensive patients studied in a similar manner after receiving a subcutaneous injection of pituitrin, a slight rise in average diastolic pressure and an equally slight fall in average systolic pressure, were observed after 20 min. The average pulse rate was unchanged.

5. In the same patient, an unusual response to the injection of pituitrin was not necessarily accompanied by a vigorous response to epinephrin.

6. No constant or frequent deviation from the reported normal cardiovascular response to the subcutaneous injection of epinephrin and pituitrin could be demonstrated in this series of patients with essential hypertension.

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**MALIGNANT NEPHROSCLEROSIS (MALIGNANT HYPERTENSION).\***

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TWENTY years have passed since Volhard and Fahr used the term, "malignant nephrosclerosis," synonymously with malignant hypertension to designate a definite clinical and pathologic disease entity involving primarily the heart, blood vessels and kidney. Much has been written in Europe, but less in America, to substantiate the existence of such a disease. It is not possible in this very brief report to mention the names of all investigators who have shown interest in this condition, yet, since the problem is primarily a vascular one, it is a pleasure to acknowledge the debt which medicine owes to such men as Bright, Johnson, Gull and Sutton, Jores, Klotz, Hübner, Volhard and Fahr, and many others who have done such important work in the field of vascular pathology.

The present conception of the vascular lesions of the kidney held by clinicians and pathologists lacks both uniformity and clearness. There appear to be three rather distinct schools of thought: first, those clinicians and pathologists who recognize a granular or contracted kidney resulting from a primary disease of the small arteries and arterioles, and who use the terms, "chronic vascular nephritis," "arteriolosclerotic disease of the kidney," or "hypertensive nephritis," but who do not attempt to differentiate those cases which Volhard and Fahr would regard as malignant nephrosclerosis from cases belonging to the much more common disease which these same authors have called benign nephrosclerosis. The second group is much smaller and is comprised of those investigators who attempt to differentiate a benign from a malignant type of hypertension, but who simply regard malignant nephrosclerosis or malignant hypertension as a terminal phase, clinically and pathologically, of a preceding benign vascular disease. A third group believes that benign and malignant nephrosclerosis both from a clinical and pathologic standpoint may appear as two separate and distinct entities; that the malignant nephrosclerosis may become superimposed on a kidney already the seat of an advanced benign nephrosclerosis, but who believe, and this is important, that patients who have benign hypertension, even though it progress to renal

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decompensation, need never show the clinical and histologic changes characteristic of malignant nephrosclerosis. In other words, this third group, which constitutes rather a minority, believes that malignant nephrosclerosis may appear independently as a distinct entity, or that it may become superimposed on the benign disease.

**Clinical Findings.** The outstanding clinical findings of malignant nephrosclerosis are a gradually rising systolic and diastolic blood pressure which is maintained far above the normal level and which is usually higher than that of benign nephrosclerosis, and tends to be more constant than in the latter disease. Associated with this hypertension are signs and symptoms referable to the heart and blood vessels, particularly the blood vessels of the choroid and retina. The heart enlarges, headaches are severe and frequent, and visual disturbances are both common and serious, for "albuminuric retinitis" is extremely important and, as Volhard and Fahr, in 1914, pointed out, it may be the earliest sign of diagnostic importance in differentiating malignant from benign nephrosclerosis. As the disease progresses the picture changes from what was primarily a cardiovascular disease to one in which the kidney changes appear to play the leading rôle. These renal signs and symptoms may appear in an acute, a subacute or chronic form, and are characterized primarily by an increasing tendency toward fixation of the specific gravity at a level of 1.010 to 1.012 (isosthenuria), a polyuria that is finally replaced by oliguria, the presence of a considerable amount of albumin, a variety of casts and the almost constant presence of red blood cells in the urine. As the disease advances there appear other signs of renal insufficiency, with an elevation of the non-protein nitrogen constituents in the blood and the presence of positive indican and xanthoprotein reactions in the urine. There is in addition increased pallor, anemia, loss of appetite, and loss of weight. If the patient does not die prematurely from cardiac or vascular disease, the end will come with uremia. Indeed, in the late stages the clinical picture is indistinguishable from that of chronic glomerulonephritis, a fact which is substantiated by autopsy records which show that approximately 65% of these patients with malignant nephrosclerosis die a uremic death. It is interesting at this point to mention that edema which is so often a striking feature of chronic glomerulonephritis is, in malignant nephrosclerosis, usually absent, and if present is almost invariably of cardiac origin. This disease is seen, as a rule, in middle-aged individuals. In 60 cases which came to autopsy the average length of life was 42 years, and of this group, females were more numerous than males.

The sequence of events in malignant nephrosclerosis, in which a cardiovascular disease appearing in younger people progresses rapidly, terminating fatally by a uremic death, and seldom running a course of more than 2 to 4 years, forms a sharp contrast to the long slow chronic course of benign nephrosclerosis seen in elderly people

in whom death most commonly occurs after a period of years through myocardial or cerebral injury.

Benign nephrosclerosis portrays itself throughout its long and chronic course as primarily a disease involving the heart and blood vessels, while any signs or symptoms referable to disturbances in kidney function stand far in the background. There is frequently substernal pressure or shortness of breath on exertion and in the later stages evidence of chronic passive congestion of the lungs, liver and kidneys with or without subcutaneous edema. The cerebral signs and symptoms vary from mild headaches, dizziness, throbbing, slight visual disturbances and confusion, weariness and failing memory, to the more severe cerebral accidents resulting from thrombosis or hemorrhage. The course is remarkably slow, and for years the patient may present no symptoms attributable to his disease or may suffer recurrent cardiac weakness. The skin is often flushed and an examination of the blood may show the red blood cells in excess of the normal. In some measure it is a disease which responds to treatment. The first danger is the heart; the second the vessels, either coronary or cerebral, and the third danger is a pulmonary complication such as bronchopneumonia. The urine shows little change in color, volume or concentration. Albumin and an abnormal sediment are usually lacking. In only 2 of 100 cases did the vascular lesion advance to such a degree as to suggest a true renal insufficiency. This benign nephrosclerosis is seen most commonly in patients above 50 years of age. In a consecutive series of 100 patients who came to autopsy, collected by one of us (H. E. M.), the ages varied from 40 to 80 years, the largest group falling between 60 and 70.

**Anatomic Findings.** The findings at the autopsy table in a patient dying of malignant nephrosclerosis may vary considerably, depending on whether the patient dies in the early stages of the disease from myocardial injury, cerebral injury, rupture of the aorta, or a complicating pneumonia, or whether the patient dies in the late stage with all the clinical signs of uremia. Of the 60 patients who came to autopsy, 35 died of uremia, many showing the classic changes with pericarditis, pharyngitis, gastro-enterocolitis, edema of the brain and lungs, and a uremic odor to all tissues. Twelve of the patients showed extensive cerebral hemorrhage, 10 died of heart failure, 2 of aortic rupture and others of pneumonia, erysipelas and septicemia. There was nothing distinctive about the habitus, although the majority were large-boned individuals varying greatly in weight. The external pallor so often recorded by the clinic corresponds to a diminution in the quantity of blood. The two organs showing the most striking changes, and the changes most valuable from a diagnostic standpoint, are the heart and kidney. The heart in this series of cases had an average weight of nearly 600 gm., the left ventricle showing a most remarkable concentric

form of hypertrophy. The kidney is usually of about normal size. It may be slightly reduced and finely granular, but more striking than the alteration in size of this organ is the congestion of both cortex and medulla and the presence of petechial hemorrhages, not only throughout the kidney, but also beneath the epithelium of the kidney pelvis.

The findings at the postmortem of patients dying with benign nephrosclerosis may be equally variable, but signs of uremia, if they do occur, are extremely uncommon. Usually in this benign nephrosclerosis there is a plethora and, while the heart and kidneys may somewhat resemble those from a patient with malignant nephrosclerosis, petechial hemorrhages within the kidney are absent. Actually, the difficulty in the differential diagnosis of far-advanced malignant nephrosclerosis is not one between this disease and the benign nephrosclerosis, but rather one between malignant nephrosclerosis and chronic glomerulonephritis. Patients with chronic glomerulonephritis will usually show a moderate hypertrophy of the left ventricle, but this is seldom to be compared to the extraordinary hypertrophy seen in malignant nephrosclerosis. It is only fair to state that if one is doing an autopsy and knows nothing at all of the preceding clinical history, it could well be impossible, from the gross anatomic standpoint alone, to differentiate a case of chronic glomerulonephritis from one of chronic malignant nephrosclerosis, since the pallor, the anemia, the signs of uremia, the hypertrophy of the left ventricle and the granular kidney showing petechial hemorrhages are common to both.

**Microscopic Findings.** The most important histologic changes in malignant nephrosclerosis are found in blood vessels, including the medium-sized muscular arteries, the small arteries and the arterioles. They are found throughout the body, but the most marked lesions are seen in the arterial tree of the kidney, and also, though to a lesser degree, in the vessels of the pancreas, capsule of the adrenal, gastro-intestinal tract, spleen, brain and fundus of the eye. There is not simply a single change in these vessels, but a variety of changes. There is hypertrophy of the vessels with marked thickening of the media and dilatation of the lumina of the larger of these vessels. This is often accompanied by a reduplication of the internal elastic lamina, and an increase in the connective tissue of the intima and adventitia (Fig. 1). In the smaller arteries and arterioles a fluid mucoid material accumulates beneath the endothelium which may increase to such a degree as to bring about apparent occlusion of the lumen. The endothelial cells of vessels showing this change are usually swollen, and occasionally a substance is seen within the cytoplasm that takes the same tinctorial reaction as the subendothelial mucoid material of the intima. The endothelial cells proliferate and enlarge, and become incorporated in this underlying ground substance (Fig. 2). Where the lesion is

older, an organizing process is seen within the thickened intima, fibrils appear within this amorphous ground substance and cells beneath the endothelium increase in number, become drawn out as spindle-like forms and arrange themselves in concentric layers separated by collagen fibrils (Fig. 3). This picture has been given a variety of names, as "fibrosis of the intima," "endarteritis obliterans" and simply "intimal swelling." It may undergo regressive changes in the form of hyaline transformation, or may show con-

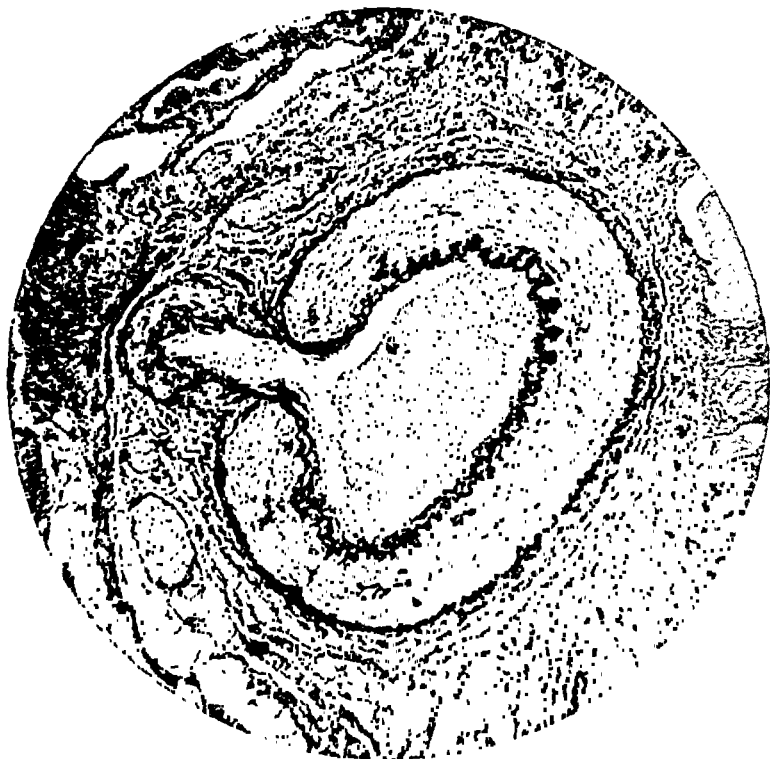


FIG. 1.—Interlobar artery from the kidney of a patient, aged 33 years, dying of malignant nephrosclerosis. Note the extraordinary vascular hypertrophy with the greatly thickened media, and the reduplication of the internal elastic lamina. A small branch, also showing medial hypertrophy, is seen at one side.

siderable lipid material, which is taken up by cells which accumulate in rows and clusters beneath the endothelium. The outcome of these changes leads to a narrowing of the lumen which far too commonly produces an apparent complete occlusion, a change which is frequently assisted by thrombosis of the lumen (Fig. 4). Another change found within the smaller arteries and arterioles in malignant nephrosclerosis, and quite the most spectacular lesion of the disease, is the marked destruction of the entire wall, with fragmentation of

the basement membrane, a separation and splitting of the layers of the vessel wall resembling a dissecting aneurysm, a saturation of the wall with red blood cells, plasma and fibrin, necrosis of muscle fibers and hemorrhage into the surrounding stroma (Fig. 5).

In the kidney these vascular lesions appear most clearly, and occur most commonly in the small lobular arteries and afferent vessels to the glomeruli. These hemorrhagic lesions of the vessels

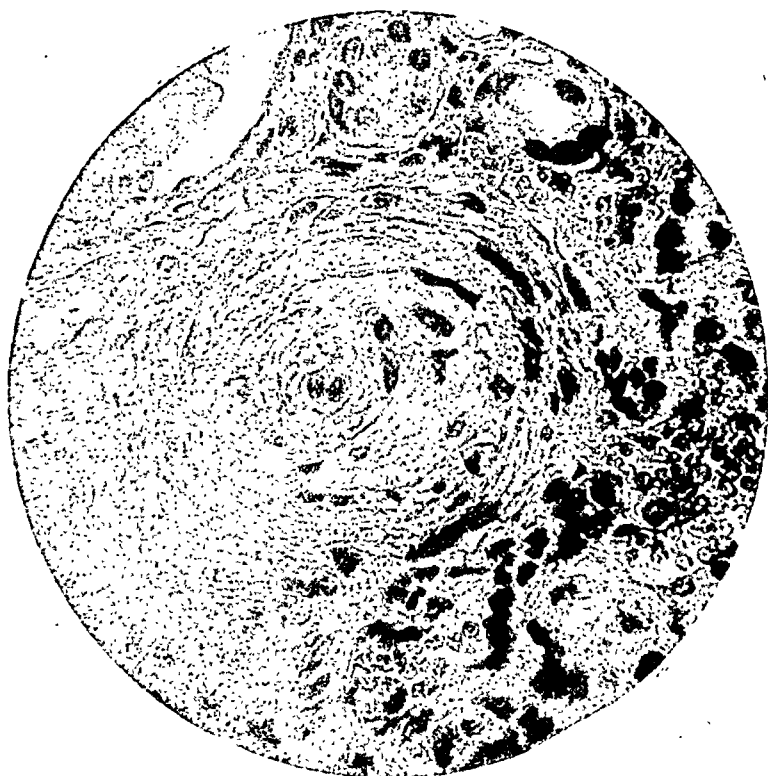


FIG. 2.—Small lobular artery of the kidney. The lumen is apparently obliterated through the extraordinary change in the intima. The intima is greatly thickened by the deposition of a mucoid ground substance containing few large ovoid cells, resembling the swollen endothelial cells at the center. In the more peripheral portion of this intimal thickening the cells appear spindle shaped and are separated by collagen fibrils. The muscular fibers of the media are replaced by connective tissue and ground substance.

are not merely a terminal event, for these are found in all stages of repair. Endothelial cells and adventitial cells, proliferating and building intercellular fibrils and ground substance often assume a nodular form which has been described as resembling a small granuloma. All of these changes described as occurring within the arterioles may be found within the capillary tuft of the glomerulus as well (Figs. 6, 7, 8 and 9). Very commonly one may trace the

changes in the wall of an afferent arteriole directly over into part or all of the capillary tuft of the glomerulus; and the glomerulus, like the arteriole, may show chronic, fresh, healing, healed and even recurrent lesions. The tubules of the kidney instead of undergoing simple atrophy and collapse may show varying types of degeneration and even necrosis (Fig. 10), and the contents of the tubule may vary from precipitated protein, fibrin, red blood cells, desquamated epithelial cells and polymorphonuclear leukocytes to

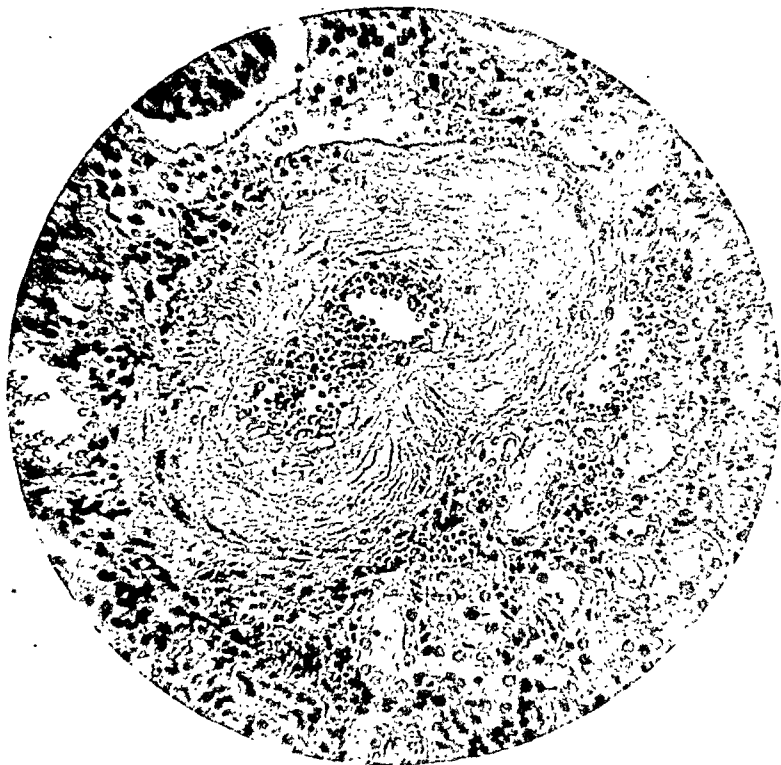


FIG. 3.—Lobular artery of the kidney. It is greatly increased in size. The muscular fibers of the media are hypertrophied and form a narrow outer border. Most striking is the marked thickening of the intima by a mucoid type of ground substance containing few cells and scattered intercellular fibrils. There is no increase in elastic tissue in the intima in this vessel.

little or nothing at all. This destruction of tubules may be very widespread and the remainder may show marked compensatory hypertrophy. In addition to these vascular, glomerular and tubular changes, the stroma of the kidney becomes greatly increased and shows signs of a chronic resorptive inflammatory reaction with foci of lymphocytes and mononuclear cells which are usually grouped in foci.

Mention has already been made of the difficulty the clinician

may have in differentiating benign from malignant nephrosclerosis during the early phase of the disease, and of the similarity at this stage in the anatomic changes seen in these two diseases at the autopsy table. Therefore, it might be well at this point to contrast briefly the histologic changes in the vessels in malignant nephrosclerosis with those of the benign disease. The localization of the vascular lesions in both diseases is the same; furthermore, the changes in the small muscular arteries which show medial hyper-

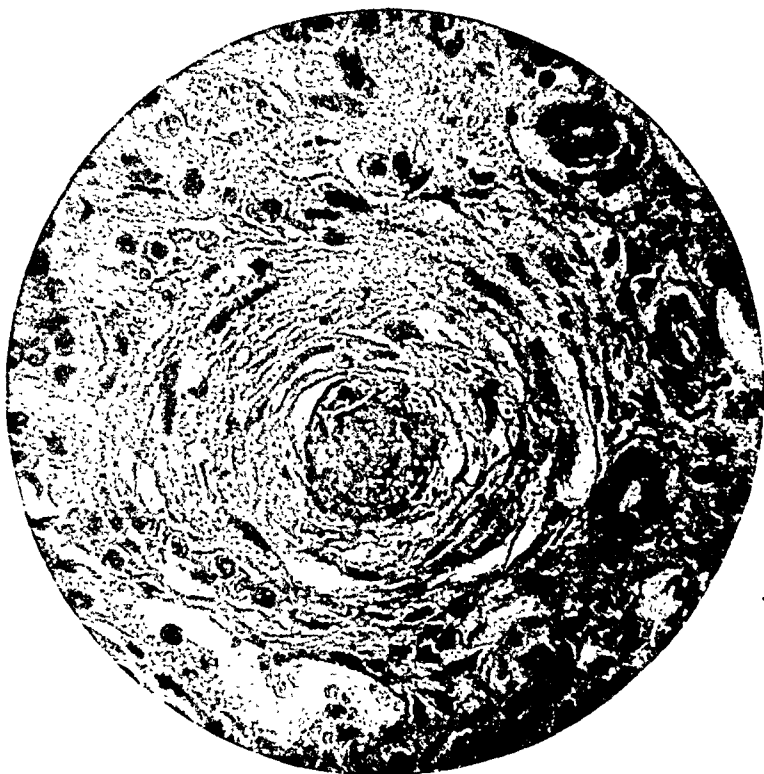


FIG. 4.—A lobular artery of the kidney. The normal architecture of the vessel wall is replaced by concentric layers of spindle cells and intercellular collagen fibrils embedded in ground substance. The endothelial cells are not visible and the lumen is occluded by a small fibrin thrombus.

trophy, intimal elastosis and connective-tissue thickening of the adventitia, are in the two diseases indistinguishable, but with this the similarity of the two diseases ceases, for in the smaller arteries and arterioles of the size of the lobular and afferent vessels of the kidney, the changes in the two diseases present a striking contrast. In benign nephrosclerosis the most constant findings comprise a swelling of the basement membrane of the arterioles which may show lipoid degeneration, and a replacement of the muscular fibers of the media by connective-tissue cells and ground substance. The

lumen of the smallest vessels is somewhat reduced and the wall would appear to have lost its ability, not alone to relax and dilate, but also to undergo any involuntary contraction. In the kidney this swelling of the basement membrane and, to a less extent, the increase in ground substance in the wall of the arteriole may be traced to the glomerulus, to the glomerulus capsule and to the tubule as well. It is common to find scattered glomeruli that have collapsed and appear as eosin-staining nodules of hyaline material.

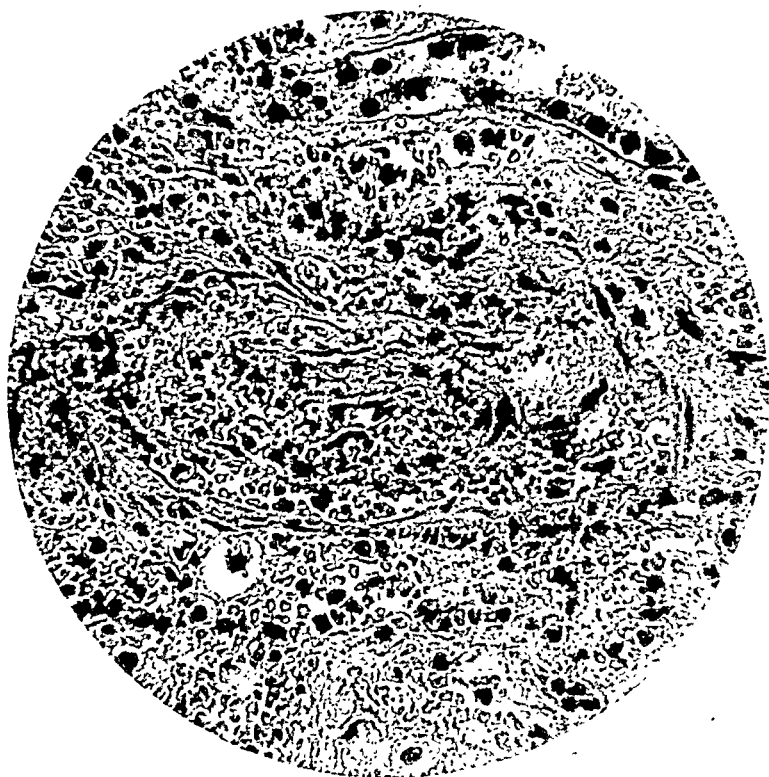


FIG. 5.—A small lobular artery of the kidney. The vessel is scarcely distinguishable through the extensive destruction of the wall. The lumen is distended with red blood cells. The walls of the vessel are broken and separated by plasma and red blood cells. There is a fresh hemorrhage into the surrounding stroma.

The corresponding tubule, even before the glomerulus shows any appreciable change, may be quite small, shrunk and collapsed. In malignant nephrosclerosis the arterioles may show all of these changes, but in addition there is the accumulation of mucoid material in the intima (Fig. 2), the endarteritis (Fig. 4) and the hemorrhage and necrosis of the wall (Fig. 5). The destructive and inflammatory lesions of the glomeruli (Figs. 6, 7, 8 and 9), tubules (Fig. 10) and stroma seen in malignant nephrosclerosis also aid in the differential diagnosis.



Since it has also been pointed out that in the late stage malignant nephrosclerosis, clinically and in the postmortem room, may simulate chronic glomerulonephritis, it is in order here to state briefly the differential points in the pathologic histology, especially within the kidney, of these two diseases. The most important lesion from the standpoint of a differential diagnosis is the change within the glomerulus. In a typical well-advanced case of chronic glomerulonephritis as many as 90% of the persisting glomeruli show varying



FIG. 6.—Glomerulus, showing a fresh and severe lesion in malignant nephrosclerosis. The glomerulus is large and many of the capillaries of the glomerular tuft are over-distended with blood. There is rupture of the basement membrane and hemorrhage into the capsular space and proximal convoluted tubule.

stages of an inflammatory reaction, whereas in malignant nephrosclerosis an equally large percentage is usually relatively intact, and shows little more than a slight increase in the size, in the number of cells and in the ground substance. The remaining 10% may show hemorrhages, degeneration, inflammation and repair. The changes in the arteries and arterioles of the kidney in chronic glomerulonephritis vary to an extreme degree—on the one hand are cases in which the vascular tree is unchanged, and on the other

hand are cases in which the vascular lesions are identical with those of malignant nephrosclerosis, including the medial hypertrophy, the lamellar elastosis, the mucoid degeneration of the intima, the endarteritis obliterans and, finally, hemorrhage, destruction and thrombosis of the wall. In general, however, the vascular lesions, within the kidney in glomerulonephritis, in contrast to malignant nephrosclerosis, play a relatively unimportant rôle. Much more



FIG. 7.—Glomerulus, in malignant nephrosclerosis, showing an older lesion than Fig. 6. There is marked dilatation of the afferent arteriole as it enters the glomerulus. The lumen of the vessels is partially thrombosed. The wall is saturated with fibrin which lies between the damaged endothelium and the stretched and fragmented basement membrane. The capillaries of the tuft are thickened by an accumulation of ground substance beneath the endothelium. While some capillaries are obliterated, others are distended with blood.

important in this consideration than the character of the lesion is a comparison of the distribution and localization of the vascular lesions in these two diseases. In glomerulonephritis the changes affecting the smaller vessels are limited in general to the kidney, and especially to the afferent vessels leading to injured glomeruli, whereas in malignant nephrosclerosis the vascular lesions are very widely spread, not only throughout the kidney, but throughout the

body as well. In the tubules one finds little that is helpful in the differential diagnosis, as the destruction and hypertrophy in both diseases may be the same. Just as glomerulonephritis may appear as an acute, a subacute or chronic disease, so may malignant nephrosclerosis show the same diversity in histologic findings.

A typical case of malignant nephrosclerosis, or benign nephrosclerosis, or chronic glomerulonephritis will offer little difficulty



FIG. 8.—Glomerulus, showing a still later stage than Fig. 7. There is still some residual fibrin in the wall of the afferent arteriole and within the structure of the glomerulus. Note the proliferation of epithelial cells of the capsule forming a narrow crescent.

clinically, at the autopsy table, or histologically in establishing a diagnosis; but it is the experience of all investigators who have made a study of these diseases that Nature does not classify as sharply and as clearly as man might wish, for one finds transitions between these diseases. The appearance of transitional forms in no way contradicts the statement that all three should be considered as separate diseases, any more than their occurrence is to be looked upon as evidence that all are different stages of the same disease.

**Etiology.** From the standpoint of etiology there are two questions to be answered. The first is: how is one to explain these histologic changes in malignant nephrosclerosis? The second is; what is the primary cause of the disease itself? To answer the first of these questions, which involves the histogenesis of the vascular lesions, several hypotheses have been advanced. The earliest of these, and the explanation given by Fahr, assumes the presence of a toxin which directly injures the vessel wall and leads to necrosis and an

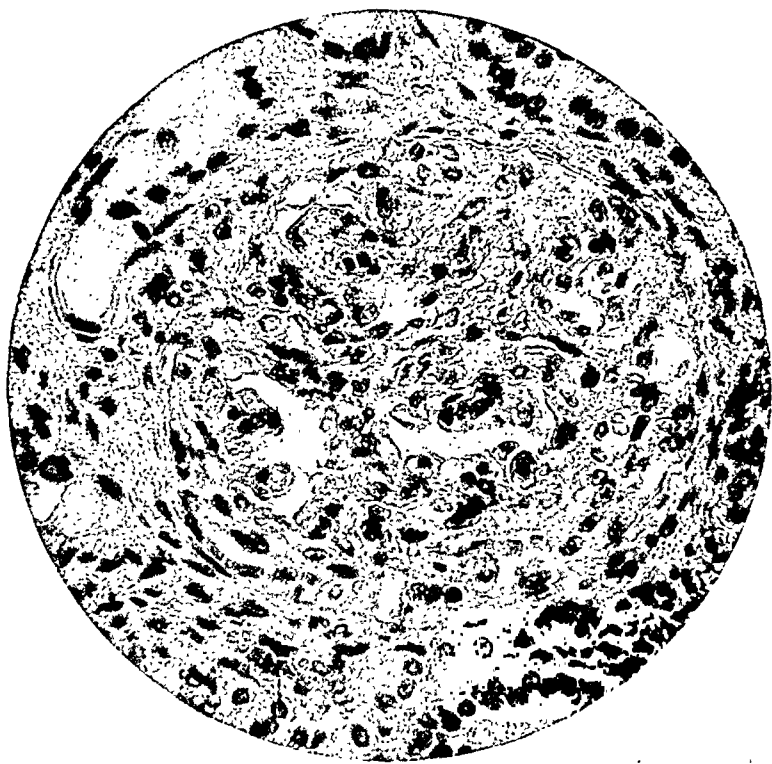


FIG. 9.—Glomerulus, showing an even later stage than Fig. 8. The capillaries of the tuft are collapsed and ischemic. The epithelial cells covering the capillaries are increased in size and number. There are adhesions between the tuft and the greatly thickened layer of capsular epithelium which forms an easily recognizable crescent.

inflammatory change. A second hypothesis, and one suggested by Volhard, considers the lesions to be the end result of prolonged ischemia through contraction of the larger arteries. A third and more recent attempt has been made to explain the changes on the basis of Ricker's observations bearing on the variability in contractility of different portions of the vascular tree. It was assumed that a stimulus sufficient to cause contraction of one segment of a vessel would lead to paralysis and dilatation of the smaller vessels

beyond, and this, if continued, would ultimately lead to changes in the vessel wall and even to necrosis and hemorrhage. The most recent attempt at an explanation is that of Schürmann and MacMahon, who consider that an injury to the endothelium, which may be very slight or very marked, is really the first and most important change. The endothelium constitutes a barrier between the blood and the tissue fluid and, when this is injured, substances from the blood may pass into the vessel wall. The quantity and quality

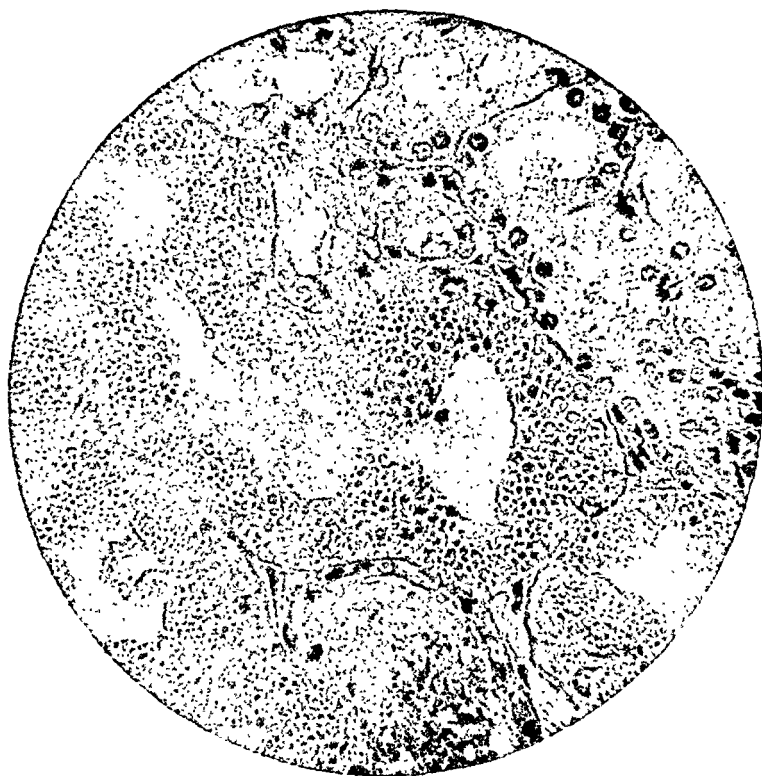


FIG. 10.—A small group of tubules from the kidney of a patient dying with malignant nephrosclerosis. The most striking change here is the droplet degeneration of the epithelium bordering the tubules.

of these substances vary with the degree of injury. If the damage is slight, these substances may be simply of a fluid nature; if, on the other hand, the damage is great and the endothelium itself is destroyed, then not only may fluids pass into the wall, but also the cellular elements. The change in the blood is almost immediate coagulation, whereas the change in the wall varies from a mucoid degeneration of the intima to fragmentation and necrosis.

In an attempt to answer the second question—namely, what is the cause of the disease itself—we have studied the clinical histories

of 60 patients who died of malignant nephrosclerosis. There seemed no constant relationship to past disease, to race, to sex or to occupation that was of great importance. Occasionally there was a story of lead poisoning, and diphtheria appeared in 2 cases shortly before the onset of hypertension. Syphilis, including prolonged mercurial treatment, has also been reported by Fahr. In addition to these external factors in the etiology, comes the probable association of some cases with disturbance in endocrine activity. There are certain cases of pituitary basophilism associated with basophilic adenoma of the pituitary, and also cases of cortical tumors of the adrenal which clinically and pathologically show malignant nephrosclerosis. Lastly, there are those cases of malignant nephrosclerosis appearing in young women, the subjects of repeated toxemias of pregnancy. This apparent lack of any one constant exogenous or endogenous factor in the etiology of this disease seems to strengthen the impression that the constitutional factor, including the age of an individual and familial or individual tendencies, plays a very important part.

**Summary.** Malignant nephrosclerosis from both a clinical and pathologic standpoint should not be looked upon as merely a progression of benign nephrosclerosis, but rather as a distinct and separate disease. It may occur alone or as a terminal complication of the benign disease. In the very early stages, when only the cardiovascular signs and symptoms are present, it may be impossible not only to say whether one is dealing with an early case of benign or malignant nephrosclerosis, but also it may be equally impossible to predict into which of these diseases the case will ultimately fall. As the disease progresses, the renal component becomes more and more conspicuous, and in the late stages it may be impossible to differentiate this disease from chronic glomerulonephritis. The etiology of benign and malignant nephrosclerosis has probably much in common, for one sees cases of chronic lead poisoning, pituitary basophilism, toxemias of pregnancy and so on, which on the one hand may show benign nephrosclerosis and on the other the much less frequent malignant disease. The course and prognosis depend not alone on the quality and quantity of the exciting agent but also in the manner in which the vessel wall responds. Where the response is of a simple degenerative nature, the disease progresses slowly, the prognosis is good and such cases are classed as benign nephrosclerosis. Where the vascular response is characterized by inflammatory changes of the intima, necrosis and hemorrhage, the course is more rapid, the prognosis is poor, and such cases are classed as malignant nephrosclerosis.

**NOTE.**—For a complete bibliography see Fahr, T., in *Handbuch der speziellen pathologischen Anatomie und Histologie*, Henke and Lubarsch, Berlin, Julius Springer, vol. 6, Pt. 1, 1925; vol. 6, Pt. 2, 1934.

## PARADOXICAL EMBOLISM.

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ALTHOUGH embolic phenomenon had been described in the 18th century and in the early part of the 19th century, the pathogenesis of embolism was not accurately observed until Virchow published his observations in 1856, which remain a model of scientific anatomic, experimental and clinical research. Equally important are Cohn's<sup>1</sup> book published in 1860 and the writings of Cohnheim in 1877.<sup>2</sup> Pulmonary and cerebral embolism now so frequently recognized and well understood were then for the first time clearly appreciated.

Emboli in the general systemic circulation supply an interesting subgroup in the consideration of embolism in general. They are derived directly from thrombi in the left heart associated with heart failure or disease of the mitral or aortic valves, and more rarely from thrombi in the aorta and large arteries, or from the pulmonary veins as a result of pulmonary lesions, such as pneumonia, abscess and gangrene, tuberculosis or tumors.

A small but distinctive group arises in association with thrombosis in the systemic veins and embolism in the general systemic circulation. In these instances the embolus passes from the right auricle to the left auricle through a patent foramen ovale, or, very rarely, through a patent interventricular septum, as reported by Louis, and has been termed a "paradoxical" (Zahn<sup>3</sup>) or "crossed" (Rostan<sup>4</sup>) embolism. Cohnheim demonstrated the first instance in 1877, observing an embolism of the right middle cerebral artery in a case of widely patent foramen ovale and with thrombosis in the veins of the lower extremities. Zahn, in 1881, reported the first necropsy finding of an embolus in transit, as it were, through a persistent foramen ovale. In 1888, Hauser<sup>5</sup> made a similar observation. Barnard,<sup>6</sup> reporting another instance of an embolus lodged in the patent foramen ovale in 1930, cited a total of 8 such instances in the literature up to that time.

The passage of tumor emboli is naturally very rare, but Zahn<sup>7</sup> reported an instance in 1889, in which there was evidence of the passage of a tumor fragment through a patent foramen ovale. In regard to the systemic circulation, it is certain that tumor cells and septic or infective emboli must necessarily be able to traverse the pulmonary capillaries without leaving evidence of pulmonary disease. It is therefore doubtful whether tumor formation or infec-

tive emboli carried through the systemic circulation necessitate any consideration of a patent foramen ovale as a route of transportation, except in the rarest instances.

About 50% of the instances of paradoxical embolism are associated with antecedent pulmonary embolism. A study of the intraauricular blood pressure establishes the pressure as somewhat higher in the left auricle than in the right, assuring competence as far as any circulation of blood from the right auricle to the left auricle is concerned in a state of health. An anatomic patency is therefore associated with a physiologic competence. Any disturbance in the pressure relationship may favor the development of paradoxical emboli when thrombosis in the venous circulation is present. Haggart and Walker<sup>8</sup> experimentally showed that a sudden occlusion of the left pulmonary artery caused an immediate rise in the pulmonary pressure of about 29%, whereas with total pulmonary occlusion the pressure increased rapidly by 120 to 257% with an immediate fall in the systemic arterial pressure.

Parkinson<sup>9</sup> reported an interesting instance of a patient who developed pulmonary infarction from an embolism during the convalescence from an operation. The patient improved for 3 weeks and then died suddenly following an attack of breathlessness. At autopsy the right ventricle was found to be dilated and showed some degree of hypertrophy, indicating to the observer that a condition of increased pressure in the pulmonary circulation had existed since the first infarction 3 weeks previously. The patient had a patent foramen ovale only 0.3 cm. in diameter and embolism of the paradoxical type had not occurred. Hence, though a foramen ovale may be present, paradoxical emboli do not necessarily occur with increased pressure in the right side of the heart, but the predisposition thereto must nevertheless be held in mind. The anatomic evidences of increased right ventricular pressure, because of the pulmonary infarction, however, were conclusive.

Patency of the foramen ovale is the commonest of all fetal relics. The literature generally recognizes the incidence of patency in all necropsies as between 30 and 35%. The uniformity of this percentage in the literature is striking.

It would appear from the literature that the size of the patency makes a great difference. In 1100 necropsies observed by Thompson and Evans<sup>10</sup> there were 319 instances of patent foramen ovale in which the opening was only large enough to admit a probe. In 67 (6%) of the total necropsies, a pencil could be admitted into the orifice. The writers conclude that it is essential that over one-third of the pulmonary circulation be depleted by pulmonary embolism to favor the establishment of a paradoxical embolus. If 50% or more of the pulmonary circulation is cut off suddenly by an embolus, death results within 10 to 30 min. Also, when pulmonary embol-



ism results, sufficiently extensive to raise the pressure in the right side of the heart and yet not so extensive as to produce sudden death, a further embolus must arrive in the right auricle from the venous system to produce a paradoxical embolus, necessarily a reduced and rare coincidence. If the embolus represents a cast of the lumen of one of the larger systemic veins, a foramen ovale must be patent to a size commensurate with the passage of an embolus of such size. The rarity of the condition can thus be appreciated and probably accounts for the scarcity of any articles in the literature. Death, evidently, not uncommonly ensues if the newly arrived embolus becomes lodged in the foramen, as the 9 reported cases show.

Diagnostically, paradoxical embolism may be assumed as occurring in life if the patient is the subject of venous thrombosis, develops an embolus in the systemic circulation and, after a careful search, has no other apparent causes for arterial embolism. If pulmonary infarction precedes the embolic accident, the diagnosis is more certain.

**Case Report.** Mrs. M., aged 74, a widow, domestic by occupation, entered St. Mary's Hospital April 16, 1934, and died April 30, 1934, under the care of Dr. R. M. Mayne.

*Present complaint* is acute pain in the right lower quadrant of the abdomen associated with hernia and accompanied by vomiting. This pain began at 7 P.M., April 16, 1934. There had been several previous attacks of hernial strangulation in the right lower quadrant reduced by a nurse at the Home where she resided, but this time the effort proved unsuccessful.

*Physical Examination.* The patient was well developed, well nourished. Examination of the head and neck was negative. The chest examination was normal except that there was a blood pressure of 170 systolic, 80 diastolic with a slight heart enlargement. However, the sounds indicated no abnormality. The abdominal examination was negative except for the strangulated hernia. The urine was normal, with occasional red blood cells. The patient was operated upon by Drs. W. G. Strobel and R. M. Mayne at 11.55 P.M., April 16, 1934. A sac containing small bowel and omentum was found, with the bowel apparently gangrenous for about 6 inches of its length. Two ileostomy tubes were inserted and the ileum exteriorized, but at the time of closure the ileum was dropped back into the abdomen with the tubes *in situ*, as the color of the loop apparently had been restored. The operation was performed under spinal and gas-ether anesthesia.

On April 17 the patient had an oxygen tent used and nasal decompression begun. The condition was good, but the postoperative temperature was 102.4° F., no doubt due to the septic factor. On the 18th the temperature was 101°. On April 21 the patient appeared to be quite well except for some disorientation, temperature 102°. On April 22 it was found that the dressing was soaked with fecal matter and evidently a fecal fistula had formed. Temperature was 102°. The face was rather drawn. On April 29, at midnight, the patient had rapid respiration, with the pulse regular, but the general appearance was very bad. Temperature 102°. Breathing became very shallow and the patient died at 12.35 A.M., April 30.

The postmortem performed by Dr. George Berdez at 2 P.M., April 30, 1934, revealed the following essential data: (1) Some edema of the ankles, especially on the right side. (2) An enterostomy wound with a fecal fistula and escape of gray-greenish mucous material. The peritoneal cavity

contained no exudate and the serosa was smooth. Beginning gangrene of a loop of the small intestine about  $1\frac{1}{2}$  feet above the ileocecal valve. (3) The pulmonary artery contained a large twisted embolus measuring 0.9 cm. in diameter. (4) The heart contained some partially clotted blood. The foramen ovale was patent to the size of a pencil and a large embolus was caught passing from the right into the left auricle through the foramen. An embolus measuring about 3 cm. in length had entered the cavity of the left auricle, but was firmly caught in the foramen by its proximal end. The pathologist thought the embolus to represent a cast of the iliac or femoral vein. The heart weighed 370 gm. The coronary arteries showed arteriosclerosis Grade II, the myocardium showing a few small areas of fibrosis. The mitral and aortic valves were slightly thickened. Left lung weighed 280 gm. The right lung weighed 380 gm. In the posterior part of both lower lobes there was an area of congestion and atelectasis. Several small recent pulmonary emboli in the branches of the pulmonary artery, especially in those leading to the atelectatic areas. The bronchi contained little mucous material. (5) Spleen normal. Kidneys slightly irregularly granular. The capsules somewhat adherent. A serous cyst 3.5 cm. in diameter in the upper part of the left kidney. Liver weighed 1150 gm. Gall bladder slightly thickened and fibrous. Bile ducts patent. Pancreas normal; stomach normal. Intestines normal except for the area about the site of the operation.

*Anatomic Diagnoses.* (1) Massive pulmonary embolus; (2) patent foramen ovale, embolism in the patent foramen ovale; (3) partial atelectasis of the lower lobes of both lungs; (4) calcified hilus glands; (5) solitary serous cyst of the left kidney; (6) arteriosclerotic kidney; (7) arteriosclerosis Grade II of the aorta; (8) edema of the ankles, especially the right; (9) status after enterostomy.

**Summary.** 1. The question of paradoxical embolus and its incidence is discussed because of its rarity and the paucity of articles on the subject in the American literature.

2. Reference is made to the occurrence of emboli lodged in the foramen ovale at the time of death and the mode of production of paradoxical emboli considered.

3. The case report is illustrative of the sequence of paradoxical emboli in the systemic circulation subsequent to venous thrombosis and in association with antecedent pulmonary embolism. It represents one of the rare instances in which an embolus is found "in transit" through the patent foramen ovale at the time of death.

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## METASTATIC MELANOCARCINOMA WITH APPARENT RECOVERY.\*

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THE following case of microscopically proven, rapidly growing melanoma is herein reported, because of its unusual clinical course and favorable response to therapy.



FIG. 1.—Melanocarcinoma developing in an irritated blue-black mole, May 8, 1929.

Since Laennec first described melanoma in the human in 1806, there has been much controversy regarding the genesis and treatment of this condition. Some clinicians believe that this condition should be left untreated; others that various methods, such as Roentgen rays, radium and surgery should be instituted. Cases have been reported without recurrence in which different methods

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of therapy had been employed. In any event the progress of different cases may vary greatly.

The following is a case of melanocarcinoma of the skin of the back with metastasis in the supraclavicular space. It had grown rapidly in the month preceding operation. Treated radically by surgery,

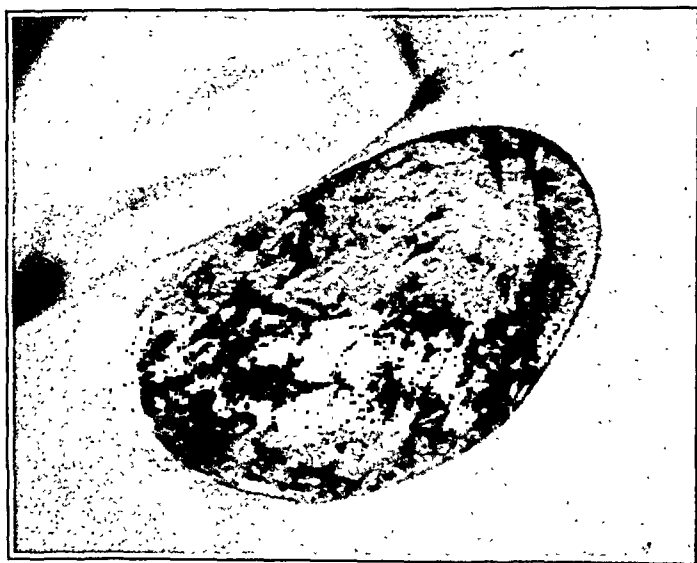


FIG. 2.—Extent of excision. In spite of this lymphatic metastases occurred. Operated July 19, 1929.



FIG. 3 —Tissue removed from back, July 19, 1929.

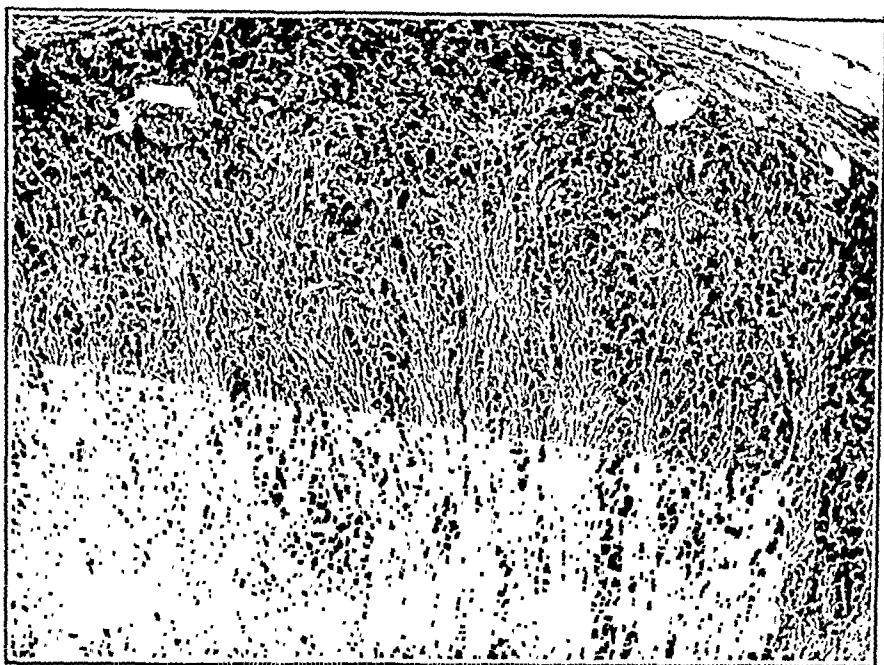


FIG. 4.—Microscopic section.



FIG. 5.—Postoperative, January 6, 1934.

Roentgen ray, and radium therapy, it has shown no recurrence  $4\frac{1}{2}$  years after treatment.



FIG. 6.—V-shaped exposure for removal of glands after closure.

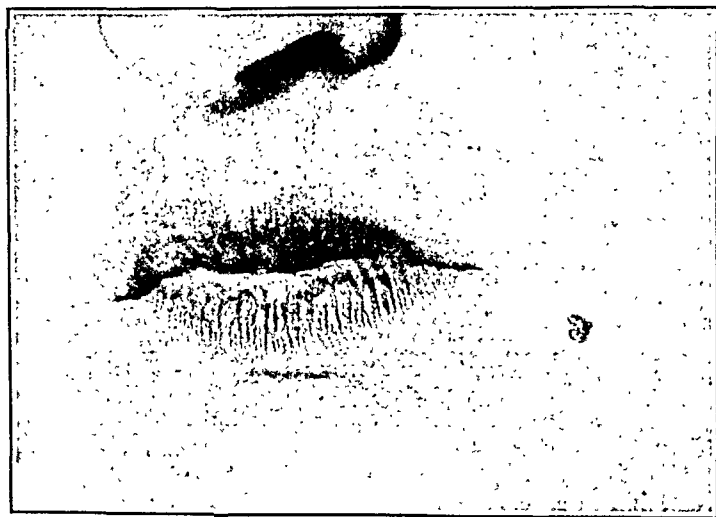


FIG. 7.—Preoperative. Melanoma on left cheek, June 16, 1929.

**Case History.** The patient, a female, aged 19 years, had always enjoyed good health. In 1929 she stated that for 4 years there was a "black spot" about the size of a pinhead situated in the left scapular region. She observed that this had become irritated as a result of continued rubbing of the shoulder straps and had grown noticeably. A physician removed the growth

with an electric needle June, 1928. Three weeks later the growth reappeared and grew more rapidly.

In May, 1929, our examination revealed on the left scapula a brownish, pigeon-egg-sized, papillomatous growth which bled easily. By means of the electrocautery knife we excised an area of skin, subcutaneous tissue, and fat 6 inches in diameter, leaving muscle tissue exposed. An application of radium was then applied to the affected area.

One month later an enlarged cervical node on the left side was removed for biopsy. The pathologic examination by Dr. Nicholas M. Alter revealed "metastatic melanocarcinoma of the lymph node." Two Roentgen ray treatments (filtered) were applied to the cervical nodes.

On July 19, 1929, Dr. R. Franklin Carter performed a plastic operation. He reported: "At the time of operation, examination revealed a large ulcerated area over the supraspinal space of left scapula, approximately 2 or 3 inches in size with numerous hard nodes in the inferior deep cervical region, nodes freely movable. Just below the angle of the mouth, left side, there was a dark papillomatous growth."



FIG. 8.—Postoperative, January 6, 1934, site of cheek lesion.

*Operation.* "Area of ulcer on back excised by triangular incision with base toward the arm, 6 by 7 inches. All tissue excised down to muscle. This space was filled by sliding an equal area from below the dress line into the area of excision. The lower space was covered with a Thiersch graft."

*Second Operation.* "Five days later, block dissection of the nose and left side of omohyoid group and all inferior deep cervicals and excision of tumor from left cheek which had been recently growing larger and becoming darker."

Following the operation the patient's wounds healed readily, except the spaces between the Thiersch graft. Pinch grafts were used to fill in these areas all of which finally healed. Keloid formation grew rapidly in all the scars and was subsequently treated by Roentgen rays. There was no post-operative Roentgen therapy directed toward possible metastasis.

Dr. Alter's pathologic report of tissue removed from the back by Dr. Carter revealed "benign chronic ulcer." The nodes of the neck on section presented melanocarcinoma. The mole from the left cheek proved to be "melanocarcinoma."

Following the operation Dr. Carter noticed a rapid enlargement of many brown moles of the usual congenital type. These assumed characteristics which were suspicious of malignant change. However, as the patient's wound healed, there was a noticeable regression of the moles. They resumed a quiescent appearance, becoming smaller and flattening out.

The patient was examined by me on January 6, 1934, at which time there was no evidence of metastasis. The wound had healed entirely and there was no evidence of a recurrence. The other moles present have retained their innocent appearance.

**Summary.** The interesting features in this case are:

1. Rapidly growing melanocarcinoma with metastasis to adjacent glands demonstrated microscopically.

2. Peculiar flare-up after removal of tumor and lymph nodes of pigmented moles on various parts of body with recession without treatment.

3. Appearance of melanocarcinoma on left cheek which was removed surgically without recurrence.

4. Patient has gained weight and has had no recurrence in 4½ years.

## MULTIGLANDULAR SYNDROMES RESEMBLING SIMMONDS' DISEASE, WITH CASE REPORT.

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THE clinical syndrome of pituitary cachexia defined by Simmonds,<sup>1</sup> in 1914, has been described infrequently since that time. A recent review by Calder,<sup>2</sup> in which he abstracts the detailed report of 37 cases by Gaubner,<sup>3</sup> in 1924, and reviews the cases published since 1924, would indicate that a total of 70 cases are on record. However, in 1933, in a more critical review, Silver could find but 41 cases which he judged on the basis of autopsy data to be examples of the syndrome. It is noteworthy that only 7 cases (Nos. 4, 5, 6, 7, 8, 9, 10) are reported in the English literature and, of these, only 3 (Nos. 5, 7, 8) were proved by autopsy data. Accordingly, it seems desirable to place on record examples of this clinical picture, particularly when postmortem findings are available.

Clinically the syndrome is seen in women in about 70% of the reported cases. It is characterized by weakness, marked loss of weight, loss of hair and teeth, trophic changes in the skin, gastrointestinal atony, achlorhydria, low blood pressure, lowered body temperature, low pulse rate and a markedly lowered basal metabolic rate. In both sexes there are striking disturbances in sexual



function, with loss of libido and potentia, with failure of spermatogenesis in the male, and amenorrhea in the female. There is usually a moderate secondary anemia and a well-marked eosinophilia. The patients are apathetic and easily exhausted. Mental disturbances are common and may dominate the clinical picture. Hypoglycemia is the rule. The disease runs a progressive course ordinarily, but may be remittent, and authentic cases, untreated, have lived as long as 44 years following the development of symptoms.

Pathologically there is a destruction of the anterior lobe of the hypophysis with secondary atrophic changes in the thyroid, suprarenal cortex and gonads, and with a decrease in the size of the thoracic and abdominal viscera. There may be a simple fibrosis of the anterior lobe with almost complete loss of cellular substance or the destruction may be secondary to tumors, cysts, syphilis, tuberculosis or trauma.



FIG. 1.—Patient in 1928.

**Case Report.** (Unit No. 55925.) The patient was a farmer (white), aged 27, native and resident of Tennessee. He had always enjoyed excellent health until 1930, when he contracted an ulceroglandular type of tularemia. He remained in bed for a month because of weakness, but soon afterward recovered his normal vigor. In 1932, he developed an infection of the right hand which was associated with fever and weakness. After a period of 1 month, the lesion was incised and healed within a short time. He felt, however, that he never regained his strength. His wife stated that he began to show personality changes at that time.

In January, 1933, he had an illness interpreted as being influenza. He then began to fail, losing weight and feeling quite worn, and noted dull frontal headaches. There were periods of fever, nausea and vomiting. He soon became bedridden. He noted that he felt cold even during warm

weather. The hair of the pubis and axillæ became thin, and he was able to go for longer periods of time without shaving. Libido and potentia were lost.

He had been married for 4 years. His wife was living and well and there had been no pregnancies, although contraceptive measures were not employed. His forebears had usually been in good health.

The patient was admitted to the medical wards on May 24, 1933, for a period of 17 days. Little improvement followed and accordingly he returned on June 29 and remained until the time of his death, on October

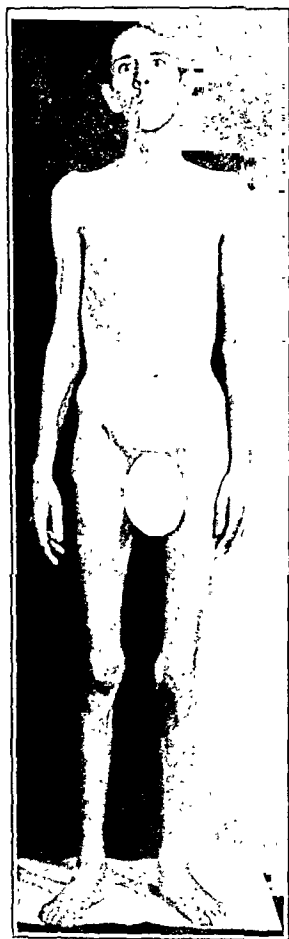


FIG. 2.—August 10, 1933.



FIG. 3.—September 20, 1933.

10, 1933. The observations obtained during the 2 admissions may be summarized as follows: emaciation was conspicuous; in January, 1933, he weighed 137 pounds (62.3 kg.), his average weight; at the time of his admission in May, 107 pounds (48.7 kg.); on June 29, 102 pounds (46.4 kg.); and at the time of his death, in October, 71 pounds (32.3 kg.), representing a total loss of 49% of the body weight. He eventually became so weak that he had to be aided in turning in bed (Figs. 1 to 4). The pulse rate was usually slow, 40 to 60 per minute, and the body temperature was also lowered—97° to 98° F. by rectum. There were frequent bouts of fever,

100° to 101° F., associated with an elevation of the pulse rate to 80 to 100. The skin was sallow, thick, wrinkled and inelastic. There was complete loss of axillary hair, marked thinning of the crines and beard, and the hair of the scalp was dry and coarse. There had been a loosening of the teeth, even the non-carious ones, but there was marked Vincent's infection of the gums. There was no general or local enlargement of lymph glands. The thyroid could not be felt. The lungs were clear to physical and roentgenologic examination. Examination of the heart revealed an extremely small organ; there were no auscultatory abnormalities, and the electrocardiograms were normal. The abdominal contents seemed normal in size and this impression was confirmed by Roentgen ray examination of the gastro-intestinal tract. The testicles were atrophic and the prostate was very small. No spermatozoa were noted in the prostatic secretion.



FIG. 4.—October 4, 1933, 6 days before death.

The neurologic examination revealed no striking abnormalities. The visual fields were normal save for a general constriction of the right field found at a single unsatisfactory examination which could not be checked, due to the patient's poor condition. He had frequent attacks of mental upsets, characterized by disorientation, delusions and hallucinations. The blood pressure was 90 systolic and 60 diastolic.

Laboratory examinations showed a moderate secondary anemia, red blood count of 3,500,000 and hemoglobin 10 gm. The total white blood count was normal, but there was a definite eosinophilia which varied between 5% and 40%. Supravital and cell volume studies did not show further abnormalities. Repeated examinations of the stools revealed no parasites, and a biopsy of a lumbar muscle showed no trichina. The urine volume was not abnormal, and the specific gravity varied between 1.003 and 1.012. There were no abnormal constituents of the sediment,

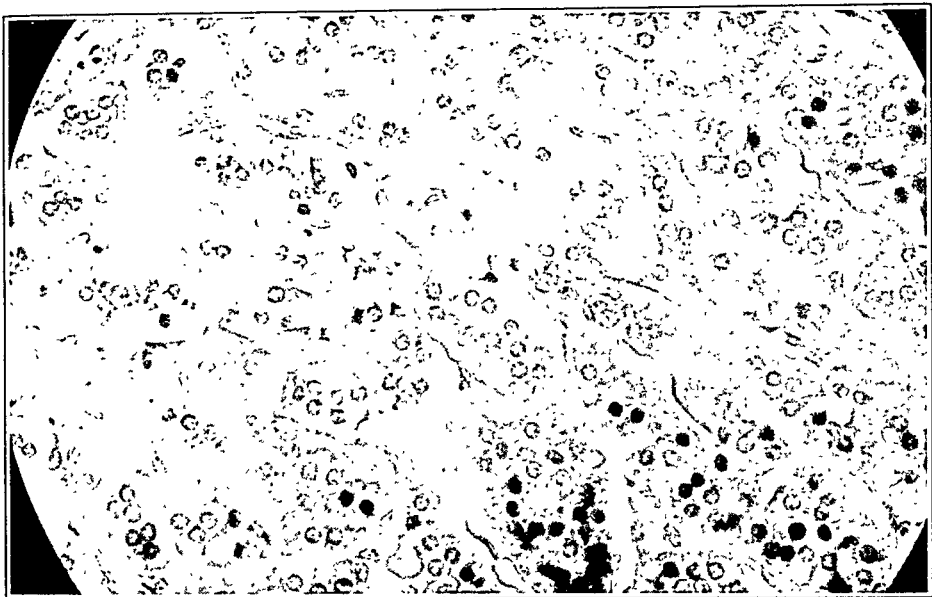


FIG. 5.—Adrenal cortex, showing vacuolization of the cells. H. and E.  $\times 450$ .

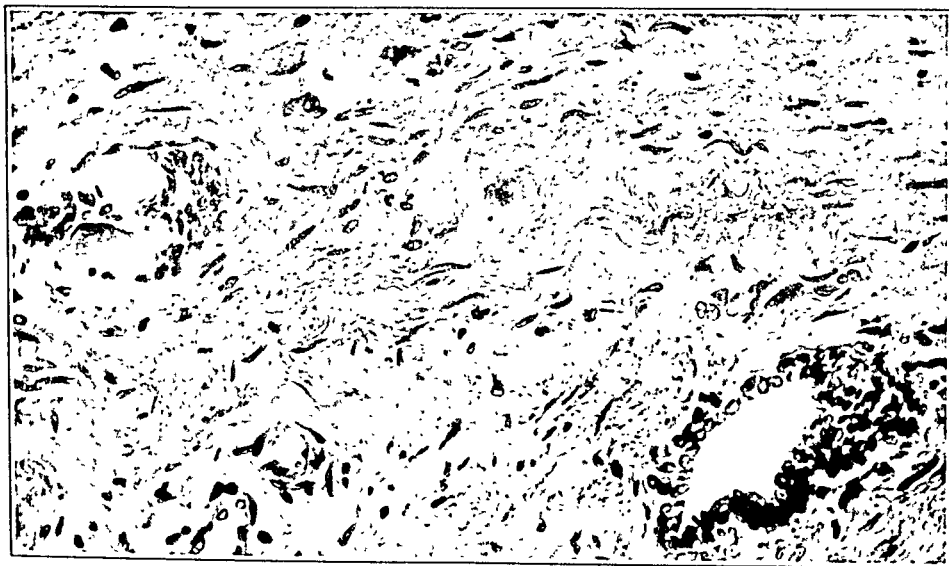


FIG. 6.—Prostate, showing the small acini and the flattened epithelium. H. and E.  $\times 450$ .

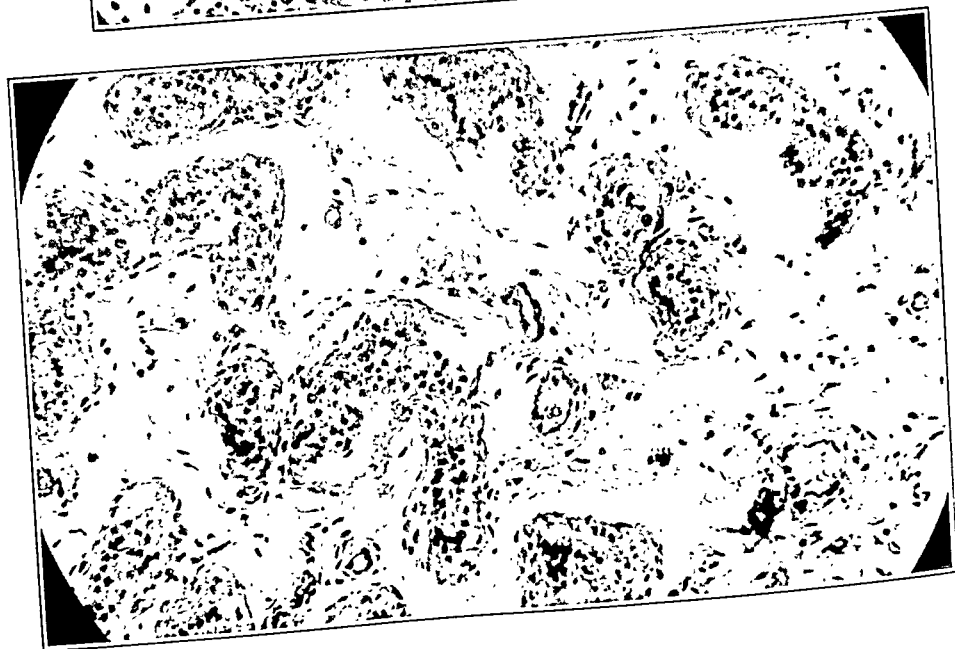


FIG. 7.—Testis, showing marked atrophy of the interstitial cells. H. and E.  $\times 225$ .

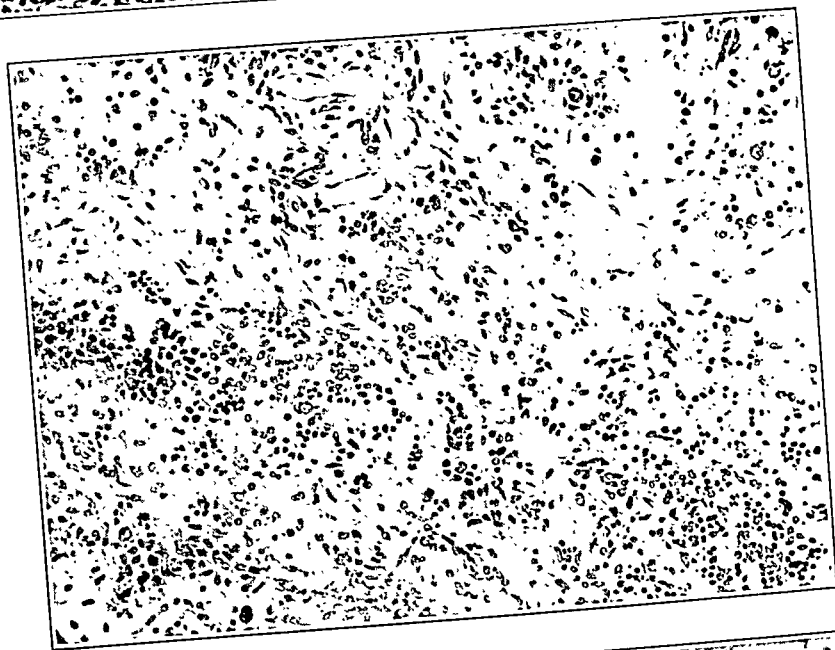


FIG. 8.—Portion of anterior pituitary showing replacement of cellular elements by fibrous tissue and invasion of the gland by neoplastic cells. H. and E.  $\times 225$ .

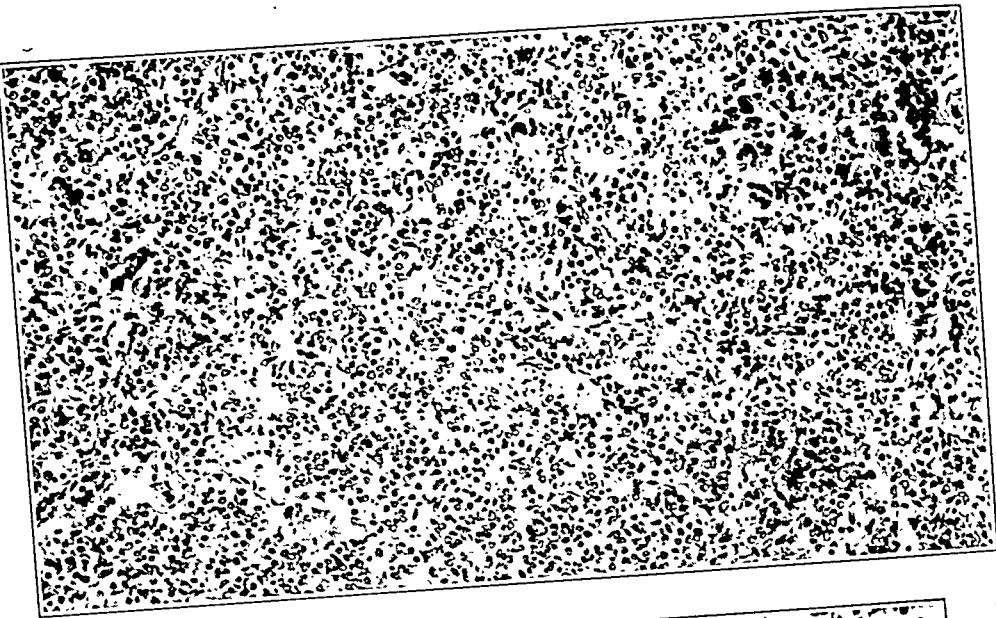


FIG. 9.—Normal area of the anterior pituitary. H. and E.  $\times 225$ .

and the tests for sugar and albumin were negative. Kidney function tests were normal, blood non-protein nitrogen was 25 mg. % and the phenol-sulphonephthalein excretion was 55% in 2 hours. There was a fasting achlorhydria, but following the injection of histamin (0.5 mg.) there was a free acid content of 25 and a total of 36 cc. of  $\frac{N}{10}$  sodium hydroxid. Roentgen ray examination revealed a normal stomach and intestinal tract. Basal metabolism studies gave readings which varied between 35% and 42% below normal. The respiratory quotient was 0.67. It is important to note that the basal metabolic rate was -34% before undernutrition became prominent. The fasting blood sugar was always low, 55 to 65 mg. %, and there was increased tolerance to ingested glucose. The blood calcium of 11.6 mg. % and the phosphorus of 3.6 mg. % were normal. Total serum protein was 6.24 gm. per 100 cc., with a normal albumin-globulin ratio. Blood cultures were sterile repeatedly. Agglutinins were present against *B. tularensis* in dilutions of 1 to 640, but all other agglutinations were negative. The Wassermann reactions on the blood and spinal fluid were negative. He was not allergic to intracutaneous injections of old tuberculin. The stereoscopic plates of the skull showed an enlarged sella turcica with thinning of the posterior clinoid processes and with evidence of pressure on the floor of the sella. These signs were interpreted as indicating the presence of a pituitary tumor.

The clinical impression was that the patient had anterior pituitary cachexia (Simmonds' disease).

An attempt was made to better the nutrition by injections of insulin, but he reacted so markedly, with the usual signs of hypoglycemia, even to small doses that they had to be discontinued. When given small amounts of thyroid extract, 90 mg. daily, the basal metabolic rate rose to +4%. At this level he was so uncomfortable that this medication was stopped; as the basal rate dropped he became comfortable again. He was also given 10 gm. of sodium chlorid a day because of possible suprarenal insufficiency. Specific substitution therapy was attempted. Saline suspensions of fresh hog pituitary, 1 mg. of which would cause ovulation in the rabbit, were prepared daily by Dr. Wolfe, of the Department of Anatomy. The patient was given 200 to 400 mg. of the material subcutaneously, daily for a week, with no recognizable effect. He was then given, subcutaneously, 10 cc. of follutein, a sex-stimulating hormone, furnished by E. R. Squibb & Sons, but no response followed, and he died 8 days after these injections were begun.

The report of the postmortem examination, performed 20 minutes after death by Dr. J. R. Dawson, Jr., is as follows:

The body is that of an extremely emaciated white male. It is still warm, and there is no lividity of the dependent parts. The skin is dry, loose and inelastic. The hair is coarse and dry; there is hardly any beard; the pubic hair is scanty; the axillary hair is absent. The penis is of normal size. There is an almost complete absence of subcutaneous fat.

All of the serous surfaces are everywhere smooth, free, pale and glistening. There is no free fluid in the abdomen, and the viscera are normally disposed. They are decreased in size to a moderate degree.

The heart is very small and weighs only 175 gm. The myocardium is dark brown in color and extremely flabby. The left ventricular myocardium measures 1.2 mm. and the right 0.3 mm. The pericardium, endocardium and valves are all normal.

The right lung weighs 300 gm. and the left 220 gm. No gross abnormalities are noted, other than areas of induration.

The gastro-intestinal tract is normal save for moderate congestion and diffuse melanosis.

The liver weighs 1070 gm. The parenchyma is brown; there is no necrosis. The gall bladder and bile ducts are normal.

The spleen weighs 100 gm. The Malpighian follicles are indistinct. The pancreas is small and weighs 65 gm. The lobules seem to be normal. The adrenals weigh 4 gm. each. They are obviously decreased in size in all dimensions. On section the cortex is scarcely 1 mm. thick, is extremely yellow and moderately opaque. The medulla is also increased in amount. No fibrosis is noted.

The right kidney weighs 127 gm. and the left 145 gm. There is moderate congestion present. The pelvic, ureteral and bladder mucosæ are edematous, dull, congested and thick.

The prostate is uniformly reduced in size. This is due chiefly to a decrease in the epithelial component without appreciable fibrosis.

Each testis weighs 10.5 gm. The tunic is not thickened. The tubules do not string out.

There is no isthmus to the thyroid gland. Total weight of the 2 lateral lobes is 20 gm. The tissue is firm and brown, and on section little colloid is present.

The parathyroids cannot be located.

The brain seems to be covered with normal dura, and the sinuses are normal. Focal grayish areas of thickening are seen in the pia arachnoid on the convexity of the brain and over the base. No superficial hemorrhages are noted. On section the lateral and third ventricles are seen to be moderately, but definitely, dilated. The foramina of Monro are similarly involved. The ependyma appears granular. The fourth ventricle is normal.

The pituitary gland lies in its normal position. It weighs 0.432 gm. Its capsule is definitely thickened. No division between the lobes is apparent. No degenerative lesions or tumefaction is noted. Fibrosis is not apparent grossly.

Microscopic notes: There is a bronchopneumonia present. The myocardial fibers are smaller than normal, and the liver and spleen are not remarkable.

No lesions are seen in the pancreas. There is no decrease in size of the islands of Langerhans. The acini in some instances are smaller than normal.

The cortical cells of the adrenals are vacuolated. Within these vacuoles are fine reddish granules. No other lesions are noted (Fig. 5).

The acini of the prostate are unbelievably small. The epithelium is very flat, and there is little secretion. There is no increase in fibrous tissue (Fig. 6).

Testes show complete atrophy of all interstitial cells without fibrosis (Fig. 7).

The thyroid alveoli are moderately decreased in size and are lined by very flat epithelium, but the colloid is normal in amount and appearance. No evidence of inflammatory reaction is seen. Parathyroid tissue was not seen in the blocks of tissue studied.

Examination of the brain by Dr. E. W. Goodpasture:

"Involving the region of the base of the third ventricle and extending into the hypophysis is an invasive, superficial, diffuse tumorous growth of large oval round or polygonal cells with vesicular nuclei and abundant well-defined cytoplasm, often discrete, not infrequently in loose groups which are intimately related in their growth with the ependyma, beneath and in which it is chiefly recognizable, infiltrating superficially into the surrounding brain tissue. There is much inflammatory almost granulomatous reaction associated with the growth. Mitotic figures are not numerous, but present. Large tumor giant cells are not infrequently seen.

"The growth extends, perhaps continuously, although grossly imperceptible, from the third ventricle beneath and in the ependyma back to the

floor of the fourth ventricle in the medulla. In places, especially the last-mentioned, the cells have the appearance of neuroglia with a few of the discrete cells intermingled.

"It is this tumorous growth which involves the hypophysis and partly destroys it. It is responsible also for the moderate internal hydrocephalus, probably narrowing the Aqueduct of Sylvius.

"As to its nature I am not at all certain, but owing to its intimate relation with the ependyma, its spread beneath it to distant parts, and the apparent transitions in form between epithelial-like, discrete cells to coarse neuroglial cells, I am inclined to a diagnosis of an Ependymal Glioma" (Fig. 8).

The pituitary gland was studied by Dr. J. Wolfe. After fixation in Regaud's fluid for 24 hours the gland was halved in a sagittal plane and then fixed for a further period of 4 days, after which it was postchromated for 8 days, washed in running water for 24 hours, dehydrated and embedded in paraffin. Both portions were cut in serial section in the horizontal plane. The right half of the gland was entirely destroyed, including posterior, intermediate and anterior lobe. The globular cells were replaced by a coarse connective tissue. The left portion of the gland was essentially normal. Cell counts were made on 11 sections at definite intervals apart. The eosinophils averaged 32%, the basophils 7% and the chromophobes 61%. All cells were normal.

Considering the gland as a whole, approximately 35% of the anterior lobe material was morphologically normal (Fig. 9).

Pathologists' conclusions: There is atrophy of the testes, prostate, seminal vesicles and thyroid without extensive fibrosis. The pituitary is invaded by a tumorous growth, probably an ependymal glioma. The prostate and seminal vesicles are of the type seen in the castrate. The viscera, in general, are reduced in size far beyond that which would be predicted for the degree of emaciation.

**Discussion.** It is important to point out that the clinical picture presented by this patient was compatible in every respect with the syndrome outlined by Simmonds, even though 30% to 35% of the anterior hypophysis remained. From the experimental observations of Smith,<sup>11</sup> we find that only 10% to 15% of the anterior pituitary gland is necessary for normal metabolism in the rat. However, we do not know what fraction of the anterior hypophysis is necessary for normal body function in the human being. In addition, one cannot say from histologic studies that glandular tissue is functioning normally.

The relationship between the observed changes in the pituitary and the repeated infections that the patient had cannot be evaluated. They may have conceivably played the part that the puerperal infection did in the original report by Simmonds, although we had no evidence that infected emboli were present.

The favorable results previously reported, particularly those by Brougher<sup>10</sup> and Calder,<sup>9</sup> are open to criticism. The case reported by Brougher had evidence of an adjacent tumor and the pituitary involvement was plainly secondary in importance. The patient studied by Calder was markedly emaciated when injections of antuitrin were begun, and he started to improve soon afterward. However, he continued to improve during the five months of



observation included in that report, even after the injections of the extract had been discontinued. If the residual pituitary function was so slight that it resulted in the clinical picture of profound emaciation, it is odd that the improvement should continue even after the substitution therapy was stopped. It is logical to believe that, in the future, substitution therapy will become practical in the treatment of this condition, particularly when the diagnosis is made before irreversible changes take place throughout the endocrine system. It is equally likely that, similar to other forms of substitution therapy, it must be continued indefinitely. The evaluation of glandular therapy is to be made with the greatest care, particularly since we are dealing with a disease which, as indicated above, undergoes periods of spontaneous remission and since patients untreated live as long as 44 years following the development of signs and symptoms of this condition.

That this patient had a pluriglandular syndrome is definite. As emphasized by Kraus,<sup>12</sup> it is usually impossible to attempt to differentiate these conditions pathologically unless the hypophysis is involved, as in this instance, by a process different from that affecting the other glands of internal secretion. In some there seems to be a primary atrophy of the pituitary with secondary changes in the structure of the other endocrine glands and disturbances of function, as described by Simmonds; in the syndrome of Lindemann there is a general atrophy of all the glands, occurring simultaneously; and in others, a sclerosis occurs in all the endocrine glands (Falta). Since the clinical manifestations of these varied conditions may be very similar, the correct prediction of the character of the pathologic changes underlying these syndromes may become a matter of chance.

**Summary.** This patient, then, presented the characteristic evidences of Simmonds' disease, yet at autopsy there remained 30% to 35% of histologically normal anterior hypophyseal tissue. In the strictest pathologic interpretation of this syndrome the patient did not present one of the features of the disease, that is, complete destruction of the anterior pituitary, but the clinical picture was so nearly identical with the previous reports that it seemed desirable, particularly in view of the careful clinical and histologic study to which this patient was subjected, to place this case on record.

**Conclusion.** 1. The history, physical findings, progress and autopsy data of a patient with Simmonds' syndrome are presented.

2. The pituitary was invaded by an ependymal glioma and atrophic changes were present in the thyroid, suprarenal cortex, testes and prostate.

3. Certain aspects of treatment of the condition are discussed.

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## ON THE ENDOGENOUS ORIGIN OF EARLY PULMONARY TUBERCULOSIS. THE ANATOMIC VIEW OF ITS CLINICAL DIAGNOSIS.

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(From the Laboratory of the Papworth Village Settlement.)

IN order to make an early diagnosis of tuberculosis it is necessary to be able to recognize the foci which introduce the common pulmonary lesion. It is also necessary to know the channels used by the tubercle bacillus, and the usual location of the foci which they produce.

The common pulmonary tuberculosis of the adult which is the subject of an early diagnosis is not the first manifestation of tuberculosis in the life of the individual concerned. The primary tuberculosis occurs during youth and heals, leaving a group of calcified lesions which are quite characteristic. Furthermore, the common pulmonary tuberculosis is not a form which follows the primary infection immediately (or after a short interval), like the generalization which in its acute form is an immediate offspring of the primary infection.

The form of tuberculosis which is the subject of our discussion develops after the primary infection has healed, without generalization. We know that the primary infection comes from outside, originating in an inhalation of droplets or dust of sputum containing bacilli into the lung; or in ingestion; or in direct inoculation into the skin, etc. It is obvious that generalization of tuberculosis develops by series of hematogenous outspreads, since it leads to a tuberculosis of bones, joints, urogenital system, meningitis, to chronic miliary outspreads in the lung, "punched cavities," etc. (Pagel, Miller). But the common tuberculosis of the adult is a

tuberculosis involving the lungs only, and proceeding by the way of the bronchi and the great channels being in connection with them like trachea, larynx, intestine. Thus it might be assumed with equal right that an exogenous or endogenous reinfection is the origin of this common form of tuberculosis, and as a matter of fact the opinion as to the origin of the isolated pulmonary tuberculosis is divided. (See Discussion, Cummins, Cobbett, Aschoff, Pagel.) One group of authors stresses an exogenous superinfection as its source (Puhl, Beitzke), another suggests an endogenous and hematogenous metastasis from old primary or postprimary foci to be the origin of the isolated pulmonary tuberculosis (Ghon, Schmincke, Wurm, Huebschmann, etc.).

It is not possible to approach successfully the question of the exogenous reinfection by anatomic investigation. There are clinical and epidemiologic data suggesting the possibility of exogenous superinfections for the development of the isolated pulmonary tuberculosis. In early cases one has found a current source of infection in the environs of the patient (Assmann, Ulrici). Further, it has been demonstrated by animal experiments that superinfection of a tuberculous—allergic—animal can produce an isolated tuberculosis of the lungs, if the primary infection was mild, *e. g.*, due to an avirulent or faintly virulent strain of tubercle bacilli (human strains in rabbits, Pagel, Cobbett; B.C.G., Aksjanzew and Krewer; leprosy bacilli, Bieling and Oelrichs).

But anatomic experience points to the endogenous reinfection as a great possibility for the development of an isolated pulmonary tuberculosis. This endogenous reinfection originates in a revival of old lesions, due to factors which diminish the resistance, such as diabetes, pregnancy, puerperium, old age, etc.

There are findings of exacerbation of the foci of an old primary complex, at the site of the primary focus of the lung as well as in the lymphatic glands. I have observed such phenomena of exacerbation in about 25% of my cases. They are much more frequent in the *glandular part* of the primary complex than in the *primary focus* of the lung itself.

Here we find the calcified foci embedded in areas of recent caseation. Such cases occur especially during *puberty* and *older age*; *e. g.*, I found in a woman, aged 88, who died from nephrosclerosis, that the *lymphatic glands* of the bifurcation of the trachea were tumefied and caseous and were the only tuberculous foci (besides a small calcified primary lesion in the upper right lobe of the lung). The recent caseous tuberculosis had developed in the environment of the old calcified primary focus in the lymphatic gland of the hilum.

The following is an example of caseous exacerbation of the old calcified primary food in the lymphatic glands during puberty. Girl, aged 15, in the beginning of the menstruation. Caseation of

the lymphatic glands of the lung hilum to a great extent, proceeding upward to the jugulum and downward *via* the posterior mediastinal lymphatic glands to the periportal glands and to the mesentery. Typical calcified primary focus in the left upper lobe. In each



FIG. 1.—Calcified foci in the lymphatic nodes of the hilum belonging to the primary complex, surrounded by areas of recent caseation (exacerbation of the old primary foci). ←, Advanced pulmonary tuberculosis.

lymphatic gland every calcified focus is surrounded by a circular area of recent caseation (caseous exacerbation) (Fig. 1). The intensity of caseation decreases according to the distance from the lymphatic glands belonging to the primary focus.

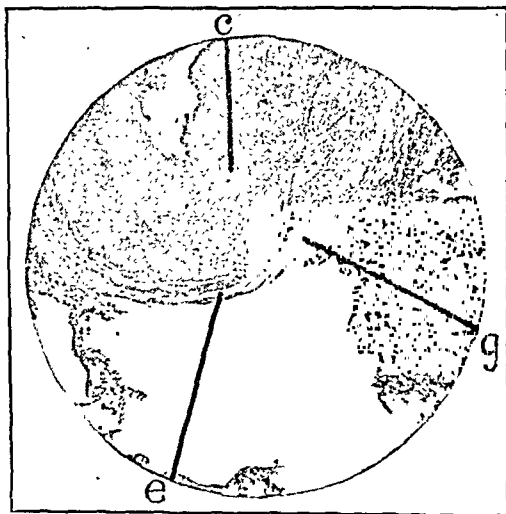
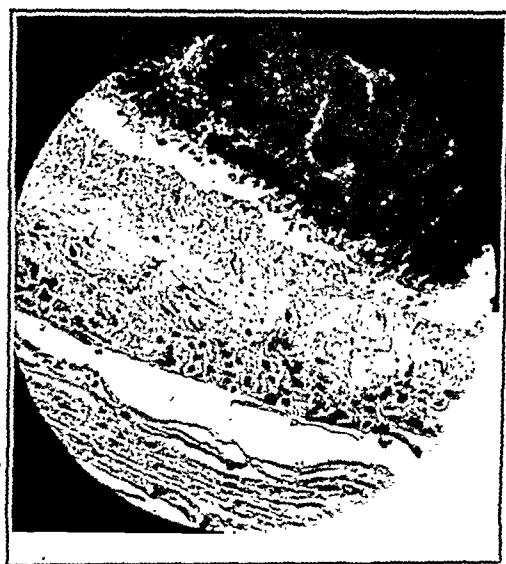


FIG. 2.—Calcified focus (c). Recent addition to the internal layers of the fibrotic capsule (e) with formation of epithelioid cells. One giant cell (g). Low power.

A recent caseation around the primary focus in the lung itself is found less frequently. We have recently seen an example of the lung of a man, aged 30, with a large cavity in the left upper lobe and advanced intestinal tuberculosis. In the left lower lobe

there was an area immediately beneath the pleura containing the old calcified primary focus of the size of a lentil as the center of a recent caseous focus of the size of a small cherry. (caseous exacerbation of an old primary focus in the lung).

The histologic examination of such foci in exacerbation demonstrates sharply confined areas of epithelioid cells recently developed, which interrupt the fibrotic capsule of a calcified focus (Figs. 2 and 3). Probably the fibrotic connective tissue of the capsule has returned to its original cellular state under the influence of the exacerbation, as described by Wurm. Or we find areas of tuberculous granulations, containing epithelioid and giant cells, invading the marginal parts of the focus and restoring the calcified caseous material (Fig. 3).



←Calcified center (C)

←Fibrotic capsule (F)

←Recent exacerbation  
with formation of epi-  
thelioid cells (E)

←Fibrotic capsule (Fc)

FIG. 3.—A calcified focus in the state of exacerbation. The calcified center (C) surrounded by a thick fibrotic capsule (F), the external part of which returned to the original cellular stage by recent exacerbation (E). The external margin of the focus consists of fibrotic connective tissue again. Higher power.

We know that about 20% of the old calcified foci of the primary complex contain living tubercle bacilli (Anders). There are also lymphatic connections of the old foci with the surrounding tissue.

So the foci of an old *primary* complex can be permanent sources for an outspread of tubercle bacilli into the blood stream.

Clear is the proof that outspreads arise from exacerbating post-primary foci.

We know that isolated regular calcified foci in the apex of the lung can be rich in living bacilli. The tubercle bacilli in such foci can be detected, after artificial removal of the calcium, as complete colonies.

After staining with Giemsa's solution I found the bacilli in such calcified foci "eosinophilic," while the bacilli are usually "basophilic." According to the behavior of the bacilli in cultures, this eosinophilic state points to an inactive state of the bacilli in calcified foci.

The calcified foci that are the subject of our discussion are due to a hematogenous outspread, because of their frequent presence in cases of chronic hematogenous generalization, during which they remain usually inactive, while they proceed by liquefaction and consequent aspiration in cases of beginning isolated pulmonary tuberculosis. There are all transitions between miliary outspreads of calcified lesions which point to their hematogenous origin and the occurrence of isolated calcified foci in the lung.

These foci may be found in the center of a larger caseous focus and there is no doubt that their exacerbation leads to the development of the larger focus which does not become the origin of a proceeding isolated tuberculosis of the lung.

E. G., a male, aged 60, showed in the apex of the right lung a large liquefying caseous infiltration of the size of a halfcrown. In the middle of the infiltration there were 3 small calcified foci of the size of a small lentil. The histologic examination showed all signs of exacerbation, such as interruption of the capsule, beginning liquefaction, etc.

The calcified foci are scattered over the lung or are confined to particular areas, especially the apex. One of our cases demonstrated a calcified focus in the "azygos" part of the left upper lobe, causing the formation of two apices of the lung. Woman, aged 26, isolated advanced pulmonary tuberculosis. Left upper lobe with abnormal division (Lob. azygos). One small yellow calcified focus in the left apex, another in the lower parts of the lobe, with a corresponding calcified focus in a bronchopulmonary lymphatic gland ("primary complex").

Another way leading from the calcified focus to the development of an isolated pulmonary tuberculosis is the aspiration of such a focus and its transmission to other parts of the lung by the bronchi.

Old calcified primary or postprimary hematogenous foci cause very often by their shrinking a small bronchiolectasis, from which the early foci of a progressive isolated pulmonary tuberculosis start. There arises then not a hematogenous form, but one which is endogenous and bronchogenic.

After liquefaction and eruption of the exacerbating calcified lesions into the "parafocal" bronchiectases, caseous material rich in tubercle bacilli is aspirated to other parts of the lung, where recent foci develop which now introduce the progressive pulmonary tuberculosis.

E. G., male, aged 36. Mother died from tuberculosis. Chronic tuberculosis the last 10 years. Avulsion of the right phrenic nerve.

Died from insufficiency of the heart. Shrinking of the right upper lobe. This is interspersed by a series of small bronchiectases, the wall of each containing a calcified focus. Similar, but not so many, lesions in the left upper lobe. Recent caseous cavity of the lower part of the left upper lobe with numerous tubercle bacilli.

EARLY (POSTPRIMARY) TUBERCULOUS FOCI OF THE LUNG AS AN INTRODUCTION TO THE COMMON ISOLATED TUBERCULOSIS OF THE ADULT.

*Hematogenous.<sup>1</sup>*

*Bronchogenous.<sup>2</sup>*

Apex . . .	<ol style="list-style-type: none"> <li>1. Discrete miliary and dense fibrous.</li> <li>2. Small calcified foci.</li> <li>3. Small bronchiectases with calcified foci in the neighborhood.</li> <li>4. Larger caseous or calcified foci ("Fruehinfiltrat" of the apex).</li> </ol>	<ol style="list-style-type: none"> <li>1. Independent exogenous superinfection of the apex (?) with caseous bronchitis ("Fruehinfiltrat" of the apex).</li> <li>2. Aspiration into the apex from a non-apical focus.</li> </ol>
Infraclavicular region <sup>3</sup>	<ol style="list-style-type: none"> <li>1. Larger caseous foci without apical lesions, so-called "Fruehinfiltrat" (precoincisous infiltration).</li> <li>2. Larger caseous foci developed at the same time with apical, subapical and horizontal location.</li> <li>3. Hematogenous caseous bronchitis.</li> </ol>	<ol style="list-style-type: none"> <li>1. Independent exogenous caseous foci and caseous bronchitis with or without other independent—apical—foci, developed at the same time from outside (typical "Fruehinfiltrat").</li> <li>2. Infraclavicular foci by aspiration from other previously developed foci, especially in apex ("Pseudofruehinfiltrat").<sup>4</sup></li> </ol>

<sup>1</sup> The proof of the hematogenous origin of all these foci is the anatomic evidence given by their presence in cases of chronic hematogenous generalization. During this period they remain usually inactive and calcify, while they proceed by liquefaction and aspiration in cases of isolated pulmonary tuberculosis. The ability of the apical hematogenous foci (1 to 4) to become the source of a progressive pulmonary tuberculosis is obvious from (a) their content of bacilli, (b) the pictures of cellular activation of the old capsule, (c) their "atheromatous" liquefaction, (d) the eruption of liquefying calcified lesions in the small bronchiectases described under 3. The apical hematogenous foci demonstrate a definite tendency to heal and to remain inactive.

<sup>2</sup> There is no anatomic evidence of the exogenous development of the foci. In animal experiments exogenous superinfection is possible, when the primary infection of the animals was due to a faintly virulent or avirulent strain of bacilli. Clinical observations of exogenous superinfection are reported.

<sup>3</sup> The foci show a tendency to become the source of daughter foci and the onset of a progressive isolated pulmonary tuberculosis.

<sup>4</sup> There are anatomic observations of such foci.

In cases of chronic hematogenous tuberculosis we usually find small cavities in the upper parts of the lung embedded in thick strata of connective tissue. They are often hidden in small fibrosed areas and may not be detected by the Roentgen ray picture. We are justified in suggesting a hematogenous origin of these small cavities. In spite of their shrinking and their concealed situation they can be the source of a bronchogenic outspread of tubercle bacilli, producing the development of recent foci in lower parts of the lung. These foci, developed by a bronchogenic outspread from

a small hematogenous cavity, become now the early infiltration introducing the isolated pulmonary tuberculosis.

So we can demonstrate by anatomic investigation in more than one way the importance of an endogenous outspread for the development of the isolated pulmonary tuberculosis.

It is an isolated hematogenous metastasis in the lung from which the process arises; the focus may itself after a period of inactivity become the center of an early infiltration or may only be the source for living virus which is conveyed from this focus to other parts of the lung by the ways of the bronchi on the bloodvessels.

It remains to discuss the usual *place* where the early foci of the isolated tuberculosis of the adult in the lung are found. The improvement of the Roentgen ray technique in the last years brought about a change in the fundamental clinical view of a very recent tuberculosis. While we formerly tried to localize the early stages of a pulmonary tuberculosis in the apex of the lung, we have now learned that the clinical onset of the disease must be looked for in other parts, especially the so-called infraclavicular region (Ulrici; Wessler and Jaches; Assmann, Redeker; Grass; Douglas, Pinner and Wolepor). I stress the clinical onset, because my autopsies show that, as a matter of fact, the first postprimary foci in cases of isolated pulmonary tuberculosis are very often found in the apex. But in spite of this fact the clinical statement is correct. The majority of the apical lesions have a tendency to become quiet and inactive, while the infraclavicular lesions, being larger, can liquefy after a short interval and, as the so-called "early cavities," may become the source of daughter foci developed by aspiration and finally of the intestinal tuberculosis resulting in the death of the patient, unless the foci within the lung have not already proved fatal. But it must be pointed out that foci in the apex are usually present, that these also may be the original source of the intraclavicular "early infiltration" or eventually, if they are large, by their liquefaction the immediate source of a progressive tuberculosis.

Usually we find in the *apical* region, *as well as* in the *infraclavicular* district, early lesions. According to the quality of these foci it seems that they have developed almost at the same time and that they are usually independent of each other.

I give two examples of such forms:

CASE 1.—Male, aged 35. Chronic hematogenous tuberculosis (advanced urogenital tuberculosis, caseous tuberculosis of both suprarenals, of the sacroiliac joint, of the second rib, transverse colon, etc.). Died from amyloidosis. Lungs: In both upper lobes in the region of the apical and horizontal branch of the posterior bronchus are well confined caseous partially calcified foci ("early infiltrations"), the apical focus being smaller than the horizontal focus, which was about the size of a halfpenny (Fig. 4). In the apex of the right lower lobe, recent caseous infiltration with the same feature. Miliary outspread in both lower lobes.



The features of the foci suggest that they are due to the same hematogenous outspread. They must have been developed at the same time independent of each other.

Besides this, the presence of a chronic hematogenous generalization and the symmetric outspread of the foci on both sides points to their hematogenous origin.

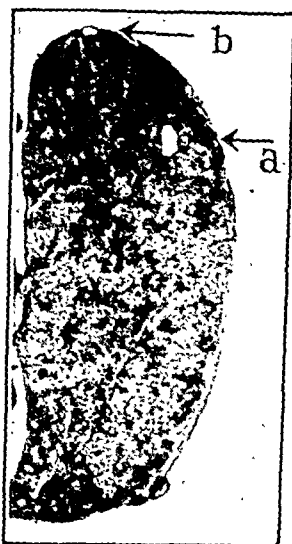


FIG. 4.—“Early infiltration” (“Assmann's focus”) (a) in the infraclavicular region (belonging to the horizontal branch of the posterior bronchus of the upper lobe), and (b) in the apex.

The *apex* was involved *as well as* the lower (“infraclavicular”) districts. If the foci are to be the origin of a progressive pulmonary tuberculosis, the larger foci in the caudal region would probably become the immediate source of aspirations by liquefaction and thus the “early infiltration.” Furthermore, it may be that the smaller apical lesions did not appear in the Roentgen ray picture. But the suggestion that the apex is not involved in such a case of early tuberculosis would not be correct.

Actually, the early foci did not proceed and did not cause metastasis by bronchogenic aspiration and thus a tuberculosis of the common type of pulmonary phthisis, because they belonged to a case of hematogenous generalization and not to the common isolated pulmonary tuberculosis. Generalization and isolated pulmonary tuberculosis being the fundamental forms of tuberculosis during the human life exclude each other (Pagel).

But the *type* of the early foci in the apical and infraclavicular areas of the lung is the *same* in cases of generalization and isolated pulmonary tuberculosis. It is only the fate of these identical foci which *differs*: in the case of generalization the tendency is to heal, to calcify and to become inactive; in the case of the common

isolated pulmonary tuberculosis the tendency is to liquefy and to proceed by bronchial aspiration.

CASE 2.—Man, aged 30. Tuberculosis of the right upper lobe with cavity. "Azygos" lobe of the left upper lobe. Deformity of the sternum which caused a deep oblong (frontal) impression in the anterior surface of the right ventricle. This was dilated in its right part, including the atrium and the part devoted to the inlet of the venous blood, while the left part of the right ventricle was stenosed.

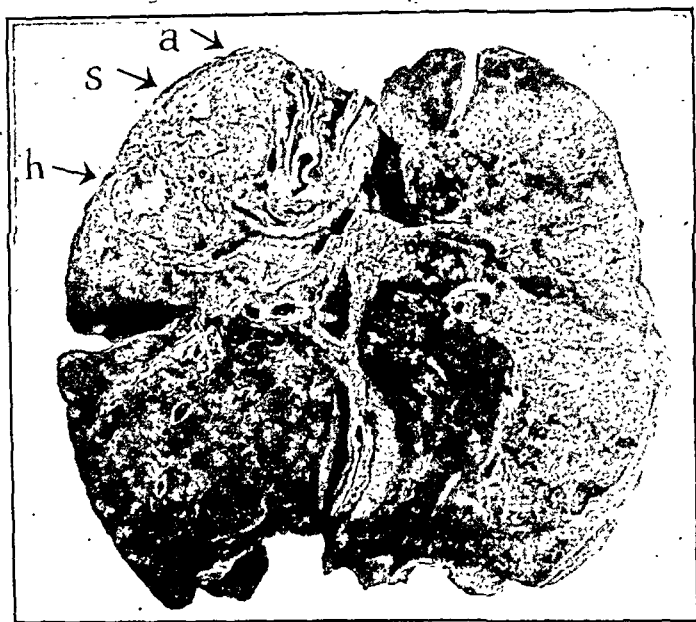


FIG. 5.—Apical (a), subapical (s), horizontal (h) early foci. The horizontal ("infraclavicular" Assmann's) focus is the largest and demonstrates an early cavity (liquefied Assmann's focus), while the apical and subapical foci are small in spite of their liquefaction. "Azygos," part of the left upper lobe (double apex). Early isolated pulmonary tuberculosis caused by deformation of the right ventricle of the heart.

This contraction of the outlet of the right ventricle may have diminished the blood supply to the lung. To this the tuberculosis of the right upper lobe may be due, just as we find tuberculosis in cases of congenital stenosis of the pulmonary artery. The tuberculosis in this case is not very advanced. The immediate cause of death was insufficiency of the heart with blood stasis to a great extent. That explains why we still find, in the right upper lobe, the foci which have introduced the tuberculosis in this case. There are foci in the three areas of the apical, subapical and horizontal bronchus of the upper lobe (Fig. 5). The horizontal focus only has a remarkable size. It is a cavity of the size of a large walnut. The foci in the apex and the subapical region are also liquefied, but much smaller in size. According to the quality of the foci (capsule,

etc.), it was obvious that all 3 foci developed at the same time, but the horizontal focus became the largest and the liquefaction was more extensive than in the other foci.

In other cases we find that one of these early foci is the metastasis of the other developed usually by aspiration, possibly by hematogenous outspread. Thus the infraclavicular "early" infiltration can be a daughter focus from an older apical lesion which revives and proceeds by bronchial aspiration. An example shows this condition clearly:

CASE 3.—Woman, aged 58. Chronic pulmonary tuberculosis. Roentgen ray picture of the chest showed nothing but a triangular shadow in the infraclavicular area of the left upper lobe. The apical region seemed to



FIG. 6.—"Early infiltrations" in the infraclavicular parts of the lung (due to an aspiration from two very small cavities like burrows made by earthworms in the apex of the posterior part of the lung. (See Fig. 7.)

be normal. The anatomic investigation demonstrated, besides typical "early" caseous infiltrations in the infraclavicular regions (apex of the lower lobe and lower parts of the upper lobe) (Fig. 6), two very small old cavities in the apical and subapical region (Fig. 7). According to the anatomic picture there is no doubt that the more caudal foci, in spite of their typical feature of "early" infiltrations, were due to an aspiration from the older apical lesions.

It should be pointed out that in such cases the Roentgen ray picture does not reveal any changes in the apical region, especially small cavities resembling burrows made by an earthworm (so-called "strand cavities" of Redeker). In other cases I have seen a fibrotic scar of the apex containing small caseous or calcified lesions which did not appear in the Roentgen ray picture while, in the same case, only the larger foci in the subapical and horizontal region were observed.

Thus, in such cases the starting point of the disease, the apical focus, has not been revealed by the Roentgen ray examination and

the clinical impression was that the tuberculosis started from an infraclavicular focus. I am sure that on account of this fact the apical onset of pulmonary tuberculosis is underrated.

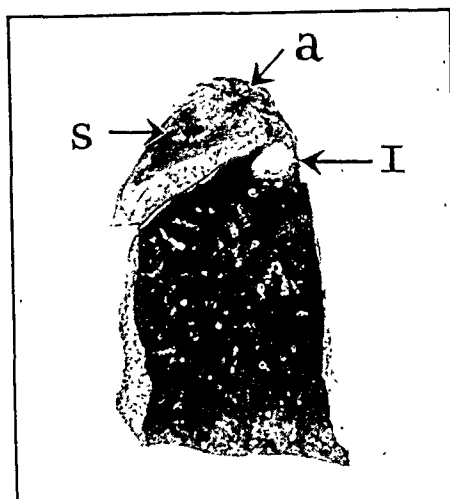


FIG. 7.—“Early infiltration” (*f*) in the apex of the right lower lobe, developed by aspiration from two small “strand cavities” in the apical (*a*) and subapical (*s*) region. Dorsal parts of the lung of the same case as given in Fig. 6.

Left upper lobe.

Left lower lobe.



FIG. 8.—Recent early infiltration near the apex (subapical region).

On the other hand, there is no doubt that independent infraclavicular foci are the sources of the tuberculosis—the apex may, or may not, be involved. It is not seldom that the early foci are in a lower position, as in the region of the horizontal bronchus of the upper lobes or near the base.

One of our cases of recent early infiltration showed a big focus near the apex but not exactly in the apical region. Its situation was between the apical and subapical district and it may be that this focus appeared in the Roentgen ray picture as an infraclavicular infiltration (Fig. 8).

Another of our cases was purely an anatomic example of an infraclavicular infiltration.

This case was of a woman, aged 36, with a recent cavity and hemorrhage in the horizontal region of the right upper lobe. Apices contained nothing but small recent nodules.

**Conclusion.** It may be concluded that all possible ways are used when a common pulmonary tuberculosis arises: the hematogenous and the exogenous or the endogenous-bronchogenous way, etc. But according to anatomic experience, the endogenous course and the revival of previous foci must be regarded as the more frequent. Similarly, foci in all parts occur when a common pulmonary tuberculosis develops. But anatomic experience demonstrates that usually the apex as well as the infraclavicular region are involved, the "infrafocus" may develop as an aspiration of the apical focus or independently. The clinical statement that the "infrafocus" has a greater tendency to become progressive than the apical focus is confirmed by the anatomic investigation. Therefore, the practitioner will very carefully observe the infraclavicular regions, but he should never neglect lesions seen in the apex, especially recent ones. Only experience and careful observation, not doctrine and theory, may help us to avoid mistakes.

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## IS THERE A "MORAL CENTER" IN THE BRAIN?\*

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WHILE reviewing a book on nervous children my attention was drawn to this surprising statement by Cameron:<sup>1</sup> "The delinquent is made, not born. The term moral imbecile is unmeaning and misleading and should be abandoned . . . there is no such a thing as a child of high intelligence who, on the point of morals only, is imbecile." Barr<sup>2</sup> says: "Now in *amoral* imbecility there is a partial or absolute absence of moral sense often as complete as in the absence of sight in the blind. This may not necessarily be associated with physical or mental defect, but it constitutes a defect of its own——."

A thumb-nail sketch of a few personalities bearing upon intelligence, emotion and morals may not be amiss. Among the "idiot savants" was "Blind Tom," a colored musician whose talent was very decided. He became famous and gave many concerts throughout America and Europe. He was born a slave and when 7 years old, the family of his master, hearing strange music, found him at the piano. He could at once reproduce the tunes he heard and repeat them after long intervals. Some of his music was from the classics and if it had been played nervously when first heard, that, too, was included in his rendering. "Blind Tom" could play a different tune with each hand at the same time, yet he was so foolish he would arise and, with his audience, applaud his own accomplishments. His intelligence was about that of a child 4 years old.

Jesse Pomeroy of Massachusetts perhaps spent more time—about 40 years—in solitary confinement than has any other prisoner in this country. His crimes began at 13 years and at 14 he was sentenced to life imprisonment and solitary confinement, only having escaped hanging by reason of his extreme youth. Within a few weeks he had stripped, trussed-up, beaten and otherwise tortured a number of little children. Because of these offenses he was detained in a reform school but good behavior procured his release after 17 months. Within the 2 months following, he tortured 2 more children, bruising, stabbing and mutilating them until they died. He made several unsuccessful attempts to escape from prison. While undergoing penal servitude tales were told of his continued cruelty and among other accusations was that of catching rats and skinning them alive. These charges were made by persons outside the prison and were never substantiated by the prison officials. Finally, Pomeroy becoming incensed, brought suit against a lady for \$5000 alleging damage to his reputation. He

\* Read before the Philadelphia Neurological Society, October 26, 1934.

scored a technical victory—the jury awarded him one dollar. Though repulsive and asocial even as a prisoner, he was intelligent. He read extensively, studied law and acquired some knowledge of several languages.

I have elsewhere referred to the following case:<sup>3</sup> A criminal of high intellectual endowment, robust and a writer of note, began to read at 3½ years and entered upon a life of crime at 9. He became an inmate of two reformatories, three county jails and a penitentiary. He loved the thrill of stealing and the night after his release from a reformatory broke into several houses. Once when arrested there were 29 charges against him including numerous thefts, kidnapping and sodomy. He said he was reared by his grandparents, was always kindly treated as a child, had attended a private school, a primary school and a college. At 21 he inherited \$34,000 which he spent in 4 years and later in life received much financial and other assistance from prominent persons; yet he had no feeling of gratitude and for his crimes no self-reproach. He once said to me: "There is a born criminal and I am one." Nor had he much faith in his fraternity, saying: "That there is honor among thieves, is the one good joke accredited to the under-world." With both statements I am in full accord. When last seen he was 48 years old, at liberty—having been granted a pardon through the intercession of many persons—and was then debating whether to return to a life of crime or accept matrimony from a woman of some culture and means. This man is highly intellectual but from his own statements and his crime record, he is an amoral imbecile.

Writing of the Englishman, Griffiths Wainewright, under the caption, "Pen, Pencil and Poison," Oscar Wilde<sup>4</sup> said: "though of an extremely artistic temperament, he followed many masters other than art, being not merely a poet, a painter and art-critic, an antiquarian and writer of prose, but also a forger of no mean or ordinary capabilities and as a subtle and secret poisoner almost without a rival in this or in any age."

At 25 years Wainewright had a long and serious period of depression. He was always exceedingly sensitive to pain, a marked contrast to his moral insensibility where others were concerned. Being a very sensuous man, he would not live without luxuries. It is not known how the strange fascination of poisoning overtook him but in some way he had learned of the lethal effect of strychnin. In dress he was dandified, indulged in perfumes and wore a number of beautiful rings in one of which strychnin was concealed. De Quincey said: "His murders were more than were ever known judicially." Through forgery he acquired control of £5000 which crime was not detected for 12 years. In 1829, having lost their own home through extravagance, Wainewright and his wife were taken into the home of his uncle, Thomas Griffiths. Sometime later the uncle died in convulsions with the married couple inheriting his property. The second victim was his mother-in-law, Mrs. Abercrombe, who with

her two daughters had been permitted to live with him. The reason for her murder is not known but it was thought she may have acquired knowledge of the dangerousness of his character. Later, Helen, a young and beautiful daughter died of symptoms similar to those of her mother. She had been murdered in the hope that the £18,000 insurance could be procured, but the insurance companies became suspicious and refused payment. After a delay of 5 years the case was heard and decided in favor of the insurance companies. Feeling unsafe, Wainewright moved to France where he lived in the home of an old man who was induced to place £3000 insurance on his life. He died some time after and, though Wainewright did not get the money, he felt he had revenged himself on an insurance company. While in France he was detained in jail for some minor offense. Being still wanted in England for forgery, through the arts of a beautiful woman used as a decoy, he was induced to return and was arrested. There were five indictments against him but he was permitted to plead guilty to two and these were not capital in nature. He was convicted and sentenced to transportation for life. While undergoing sentence he would boast of his cleverness as a poisoner and actually made two more attempts to poison persons who had offended him. Havelock Ellis said Lombroso and others would consider Wainewright a "born criminal" or a "congenital criminal" but he preferred the term "instinctive criminal."

Seemingly, as atrocious an intellectual man as ever lived was Gilles de Rais, the original of Bluebeard in the Mother Goose story. Born in a French family of high rank and wealth, this iniquitous monster of the 15th century had all the educational advantages of that time. He could speak three languages and manifested great interest in military matters. At 16 he married, the chief attraction being the wealthy estates of his wife's family. She being a relative of the 4th degree, the Church declared the marriage void, a circumstance that did not for the moment disturb de Rais. Becoming disgusted with his wife, he provided for her maintenance in another part of the castle but upon learning she was pregnant and fearing the embarrassment of an illegitimate heir, he successfully approached the Church, another ceremony was performed and the difficulty thus obviated. Unfortunately, the child proved to be a girl which so angered de Rais that he lost all interest in mother and daughter. In the struggle of Charles VII against England, he rendered distinguished service, fighting beside the Maid of Orleans and later, with others, strove hard to disprove the charges that were paving the way to her cruel death. At 25 he had achieved the high distinction of Marshal of France and retired to his estates. At that period those who dared dispute the doctrines of the Church were punished most severely. Many pleasures were denounced as the work of the devil and their prohibition led to much revolt. It has been believed that these ecclesiastical rigors resulted in the formation of some of the medieval cults giving rise to devil-worship wherein all kinds of



pleasures were indulged and atrocities committed. Books telling of witchcraft, incantations and black magic were read freely. From the undisputed evidence presented at de Rais' subsequent trial, it is believed he may have belonged to one of the most sophisticated, licentious and sadistic of these cults.<sup>5</sup> Be that as it may, there is abundant, well-authenticated historic record of the atrocious orgies in which he and others indulged. At 28, after having been away from his estates for some time, he returned and promptly banished his wife and daughter. Then began the dissipation of his vast fortune wherein he vied with the King in the grandeur of his surroundings. Among others who were invited to join him were two priests, one being his cousin. The assemblage then gathered included artists, actors, poets, musicians, designers, illustrators, astrologers, magicians and others. There was a chapel, a choir and also a laboratory for research in alchemy. The castle was surrounded by a big and ferocious guard while within drinking, carousing and the worst of atrocities were being indulged. Worship of the evil forces called for much human sacrifice. Most of the victims were boys who were trussed-up, cut, slashed and otherwise tortured to death. Such iniquities could not go on forever and the Church finally found him guilty of heresy. The civil authorities then assumed charge, brought him to trial when it was proven that there had been kidnapped or otherwise enticed to his castles 140 children, though the actual number was believed to be much larger. "de Rais was culpable of crimes so horrible that they could be read in open court only if rendered in the Latin tongue."<sup>6</sup> He made full confession, was hanged and the body burned.

Through disease, injury and shock the mind may be strangely affected and this is not recent knowledge, since Oliver Wendell Holmes reminds us that, "A profligate mentioned by Plutarch had a fall and struck his head, after which, he became a virtuous citizen." Lombroso<sup>7</sup> mentions several instances: "Gratry, a mediocre singer, became a great master after a beam had fractured his skull. Mabilin, almost an idiot from childhood, fell down a stair-case at 26 and so badly injured his skull that it had to be trephined; after this he displayed the characteristics of genius. Gall, who narrates this fact, knew a Dane who had been a half idiot, who became intelligent at the age of 13, after having rolled headforemost down a stair-case. Wallenstein was looked upon as a fool until one day he fell out of a window, and henceforward began to show marked ability."

Some years ago a local surgeon was attempting to increase the cranial capacity of bad boys by means of an incision into the skull; it was his belief that their badness resulted from cramped quarters occupied by the brain. I knew one of his "cures" who was twice afterward in the Eastern State Penitentiary and later an inmate of a jail in New Jersey. *Apropos* of that surgeon's procedure, Dr. Lloyd queried: "Does the good man think he can improve the quality of a nut by boring a hole in its shell?" Another of these

boys had headache, a vicious temper and was a truant. The mother said he had once fallen in front of a railroad train and sustained an injury which she was sure had caused his waywardness. A slight depression was in evidence in front of the skull and this was thought to be the cause of his delinquencies. Two operations were performed and soon after he was an inmate in a reformatory, later a county jail and finally a penitentiary. From the last of these institutions he made a sensational escape by burying himself beneath a cart-load of ashes; shortly after reaching the street he arose, Phoenix-like, and it was not until 6 months later that he was apprehended in California. There is a group of children dubbed the "Apache type" who, in the chronic stage of encephalitis, commit a series of misdemeanors, more or less severe. Recently, Grossman<sup>8</sup> has recorded the case of a very unruly child who became docile after epidemic encephalitis.

Under Constitutional Immorality, Tanzi,<sup>9</sup> discussing the type of individuals that show the permanent insensibility of the ruthless immoral, says: "It is more evident from early childhood, because it is more impressing, notwithstanding the negative nature of its manifestations. In youth, these persons who are immoral through deficiency of sensibility show affection for no one. In their amusements they are placid, silent and cruel. . . . They are not mortified by reproof or humiliated when caught in the act of doing wrong. . . . They neither understand nor value the generous impulses of others; they are skeptical, distrustful and malicious. . . . As there are dogs without the power of scent and flowers without perfume, so also there are individuals devoid of benevolence and sympathy."

There is abundant evidence that the two components of our mentality, intellectual and emotional, need not develop harmoniously. One may be greatly in excess and either may show infantilism. Again, disease or injury of the brain may affect one with little or perhaps no effect upon the other. Hence, "moral imbecile," "amoral imbecile," the "born, congenital, hereditary or instinctive criminal" or "constitutional immorality" are justifiable terms, in the sense that they represent a demonstrable condition, though it is debatable which designation is preferable. Browning,<sup>10</sup> in his analysis of 11 cases of cranial traumata followed by serious moral deterioration but with intellectual integrity, located a "moral center" in the right frontal lobe in right-handed persons. He was convinced that lesions of the first frontal convolution gave rise to irritability, violence and loss of inhibitory power; that lesions of the second and third convolutions gave loss of the "moral sense" leading to absence of shame, fear, sense of duty, and so on. Lehman, quoted by Eng,<sup>11</sup> believes the same brain cells can perform the functions of the intellectual and the emotional processes. Thalbitzer's hypothesis is that there is a particular emotion center and with this Eng<sup>12</sup> is inclined to agree. It is suggested by Piéron,<sup>13</sup> that undifferentiated

emotional reactions may arise at the thalamic level and then be subjected to the discriminating associative intellectual processes at the cortical level.

In regard to a "moral center": Is the cerebral cortex to be regarded as functioning in such a way that local disease or injury could only affect its activity as a whole? Or are there anatomic concentrations, so-called centers, where thought is definitely discriminate, giving such functions as attention, memory, judgment, ideation, special talent, ethical concept, etc.? We have some definite knowledge of motor centers and to a less extent those of sensation, speech and the special senses. However, intellectual and emotional centers are not so easily identified and much more data are needed if we are to be able to establish them.

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### THE RECURRENCE OF FACIAL PARALYSIS.\*

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THE purpose of presenting the following cases is to call attention once more to the fairly common tendency of the facial nerve to be subject to a recurring paralysis. Of all the nerves the facial nerve

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is the most susceptible to paralysis: this marked susceptibility as contrasted with other somatic nerves is reflected in the tendency of the paralysis to recur again either on the same or the opposite half of the face. This tendency is not recognized by medical men in general, and often the "neurologist" is not aware of this possibility. It is not mentioned by the authors of modern textbooks dealing with the nervous system.

Oppenheim<sup>1</sup> mentions briefly, "The fact should be noted that facial paralysis, both the rheumatic and the other forms, may relapse; the relapse more often affects the nerve of the other side so that the term is not correct."

A very complete discussion of recurring facial paralysis is given by Bernhard;<sup>2</sup> Huet and Lejonne<sup>3</sup> report a patient with 3 distinct attacks. Langmead<sup>4</sup> reported an instance of a girl with 3 distinct attacks of facial paralysis, always noted in the morning. A very unusual instance of recurring facial paralysis is reported by Mouriquand *et al.*<sup>5</sup> They recite the case of a girl who had 8 distinct attacks within a 2-year period.<sup>5</sup> Orbison<sup>6</sup> reported 2 cases from Dr. Spiller's Clinic.

According to Gowers,<sup>7</sup> "Second attacks of facial paralysis are rare. I have notes on only 5 instances."

The following 19 cases are divided arbitrarily into several groups: The first group consists of those cases which were examined and treated by me in both of their attacks. The first 2 cases were unusual in that they had both halves of the face paralyzed nearly at the same time, a definite period of time separating the onset on both sides.

Bilateral facial paralysis caused by known factors, such as alcohol, arsenic, toxins, syphilis, etc., is not unknown. The occurrence of a bilateral facial palsy of the so-called pure Bell's type, the connotation of which is, "a paralysis of undetermined origin," is fairly rare. According to Gowers,<sup>8</sup> "Fallopian neuritis scarcely ever occurs on both sides simultaneously, although I have more than once known a second attack on the other side to occur within a few months of the first." Harris<sup>9</sup> observes, "Bilateral facial paralysis may occur alone as a double Bell's palsy, though usually there is an interval either of months or years between the affection of the two sides."

**Case Reports.** CASE 1.—(B.H. No. 18384.) L. C., a large, heavy negro girl, aged 18, was first seen by me, January 18, 1928. At this time, she presented a definite left peripheral facial palsy. It was first observed a few days before by the girl's mother because the girl's face was twisted. As the day wore on the patient became more conscious of her trouble and complained of pain behind the ear and down the neck. While the left face was being observed the right face became completely paralyzed on March 18. She lost the sense of taste completely on both sides and with it her appetite. As a result she lost about 40 pounds in weight up to July 31, 1928. The blood Wassermann test was negative. Spinal

fluid examination revealed perfectly normal findings. Roentgen-ray of skull and mastoids was normal. No focus of infection was observed. The right half of the face recovered completely while the left remained in a somewhat contracted state.

CASE 2.—(M.E.H. No. 3252.) Anna Q., aged 11, was first seen, July 19, 1932. On June 24, the left face first became paralyzed. The previous day she had been riding in a car with a breeze blowing in her face. She had also been sitting in a draught in a movie theatre. On July 17, she went in swimming in the ocean. That same evening the right face became completely paralyzed. She had no subjective symptoms. Taste was intact. Tonsillectomy had been performed 2 years previously. General health was excellent. She was observed at regular intervals up to June, 1933. There has been a distinct improvement, although the left face still shows weakness.

CASE 3.—(B.H. No. 85560.) Mrs. G. B., housewife, aged 42, was first seen in the dispensary, December 19, 1929, with a paralysis of the right face of 7 days' duration. It was sudden in onset and accompanied by pain in the face; "I was exposed to a draught." In about 7 weeks she had recovered completely. This first attack was attended with considerable anxiety. On October 14, 1930, the patient again returned to the dispensary. At this time the left face was completely paralyzed. Not realizing for the moment that this was a different seizure, I asked her how her face was getting along. She answered, "Why, doctor, this is a brand new spell," and was quite surprised that I did not realize this fact. She was not at all alarmed on the second occasion. The left face felt stiff. She also complained of pains in the left side of the neck. This paralysis recovered in a very short time.

CASE 4.—(B.H. No. 44667.) F. H., male, aged 28, on October 25, 1927, developed a right facial palsy. He had no pain, but complained of peculiar feeling in the right face. The right half of the tongue felt numb. Recovery was complete. Three years later, December 9, 1930, he returned with the left half of the face paralyzed. As in the case described above, a similar mistake was made. In scanning the chart hastily, it was thought that this was the same attack previously treated. I was pleasantly surprised to learn that this was a different attack. Two days before the onset of paralysis, the left half of the tongue felt numb and thick. Pain was experienced anterior to the ear around the left border of the jaw. Occasional twitchings of the left face occurred. Objectively the sense of taste was lost on the left. There was no subjective taste disturbance. The face recovered completely by January 20, 1931.

CASE 5.—(M.E.H. No. 3513.) S. O., male, aged 32, was first examined, February 9, 1929, because of a right Bell's palsy which had developed on January 22. The right face had improved considerably on March 16. On March 19, the left face became completely paralyzed. He was very much upset. The possibility of a second attack had not been mentioned. He felt that he had been "let down." He suffered much more with this second attack. Pain was complained of behind the ear over the mastoid area. Tinnitus in the left ear and a very annoying persistent taste in the mouth were distressing.

The above 5 cases all had the second attacks of facial paralysis on the opposite half of the face. In all, the blood Wassermann test was normal. Also, urinalysis revealed no abnormal findings. No demonstrable focus of infection could be elicited. No case complained of blisters in the ear or of a watery discharge from the ear.

In the second group are included those patients in whom 1 attack was witnessed by me, who gave a trustworthy history of a preceding attack. It is noteworthy that patients with a second attack are not so apt to be disturbed emotionally by the renewed insult.

Cases with second attack on same side (relapse):

CASE 6.—(N.Y.U. No. 580.) M. G., female, aged 25. Left peripheral facial paralysis. Not at all upset by the occurrence. She gave a history of pains "about over the left mastoid process" and had noted a distinct disturbance of taste at the time of onset. Seven years previously, at the age of 18, she had had an attack of facial paralysis on the same side of the face. Her face returned to normal in a comparatively brief period.

CASE 7.—(N.Y.U. No. 1703.) W. L., male, aged 50, reported with a right peripheral facial palsy. There was loss of taste, subjective and objective. This patient reported a definite attack on the same side of face 4 years ago. This recovered completely.

CASE 8.—(B.H. No. 112681 D.) L. T., female, aged 18, presented a complete right peripheral facial paralysis, with insidious outset. No pain was complained of. She had noticed a disturbance of taste. Loss of taste on this side was proven by testing. According to her mother, and also well remembered by the patient, she had had an attack of peripheral facial palsy on the same side 8 years earlier, which recovered completely. It is of interest that a sister also had a Bell's palsy.

CASE 9.—(B.H. No. 11990.) S. O., male, aged 20, reported to the dispensary for treatment of a left facial paralysis. This palsy was noticed a few days ago. The preceding day he had noticed pain behind the left ear and a tendency to watering of the left eye. The weakness was first found out in the morning on arising. He did not complain of any change in taste. Testing showed loss of taste on the left anterior portion of the tongue. Two years before, this patient had had a similar attack on the same side of the face. According to the patient, this paralysis cleared up almost completely.

CASE 10.—(B.H. No. 133139.) M. I., male, aged 23, was seen, July 5, 1932. The present attack began a week earlier and was rather insidious in onset. Two days previously he had noticed pain just below the left ear at the angle of the jaw. There was no subjective taste disturbance. He was unable to detect sugar solution on the left half of the tongue. Taste was normal on the right. This patient, on questioning, revealed a previous attack on the same side 6 years before. He recovered completely in a "fairly short" period of time.

CASE 11.—(B.H. No. 19603.) E. S., male, aged 35, was seen, in 1926, with a weakness of the right face. He had a mild pain in the right occipital area, but no other subjective complaints or objective findings. He recovered completely. The patient observed that, in 1917, he had had a similar attack on the same side. As far as he could recall, his present symptoms were the same as those of the former attack.

CASE 12.—(B.H. No. 72954.) M. Z., male, aged 63, was admitted to clinic with a left facial palsy. This began on April 29, 1929. As occurs in many cases, he went to bed feeling perfectly well and awoke in the morning with the facial palsy. The blood pressure was 152 systolic and 98 diastolic. The patient remarked that 30 years ago, in Glasgow, Scotland, he had had a similar attack on the same side of the face. He soon became well. As a consequence he was not at all disturbed by his present attack.

CASE 13.—(Private patient.) J. C., female, aged 21, was seen on June 16, 1929, suffering from a right peripheral facial paralysis, ushered in with pain back of the right ear over the mastoid, arousing a fear of "mastoiditis."

The following day, while working in her office, she found that her mouth did not function properly. She looked into a mirror and found her face was "crooked." She complained of a brassy taste in her mouth. She has had tonsillitis each year for the past 3 years, but recovered completely in 1 month. In 1923, she had a similar attack on the left side of her face, which lasted 2 months, with complete recovery. This attack, in the words of the patient, was worse than the present one.

CASE 14.—(Private patient.) R. F., female, aged 23 (Italian). The third and present attack (right side) began, May 7, 1933, with "a greasy taste" on the right side of mouth. Two days later the right half of face was very painful, including the ear. The patient's first attack occurred in May, 1925, on left half of the face and lasted 1 month. She had a peculiar taste in the left half of the mouth. "I always get a greasy taste in my mouth several days before the attack begins." The second attack on left half of face began in 1930, in the spring. It lasted for 3 weeks. She experienced no pain.

CASE 15.—(B.H. No. 165555.) G. R., male, aged 84, experienced an attack of facial paralysis on the right side 30 years ago, coming on "during the night during a severe thunderstorm." He recovered in 1 week. The second and present attack began 3 weeks ago: "I went to the barber's and had my hair cut. The next few days I noticed a few lumps on the back of my neck and back of my ear. Scabs formed over these (?) lumps. At the same time my right face became paralyzed and it has been paralyzed ever since." Taste was lost completely on the right. He shows a complete right facial (peripheral type), is unable to taste sugar on the right half of the tongue, but does so on the left. There is marked weakness of the orbicularis oculi.

Cases with second attack on opposite sides (associated with diabetes):

CASE 16.—(N.Y.U. No. 693.) P. C., male, aged 56, was seen with a left peripheral facial palsy which recovered in 6 weeks. At this time he was being treated for diabetes: urinary sugar, +; blood pressure, 140/80. He gave a reliable history of a previous attack 12 years before, with a complete recovery. Patient remarks that he has had a successful operation (Talma) for alcoholic cirrhosis of the liver, 10 years ago. He has taken no alcohol since then. The first attack may have been due to alcohol, but the second was a pure Bell type.

CASE 17.—(M.E.H. No. 10998.) A. L., female, aged 60, reported to the clinic, June 14, 1928, with a left peripheral facial weakness. She was receiving treatment for diabetes at the time: urinary sugar, 3.3%; blood sugar, 321 mg. This was her third attack of this nature. In 1925, her right face was paralyzed for a time, and again 2 years ago, in 1926, the left side was paralyzed, but recovered (same side of face is involved at this time).

Cases of recurrent facial palsy, 1 attack of which was not strictly a so-called Bell's palsy:

CASE 18.—(N.Y.U. No. 1315.) C. O., female, aged 29, reported to the clinic with a definite paralysis of the left face with contracture. Her paralysis was of 3 years' duration. The patient had been suffering from a chronic discharging ear on the left. (This case is not strictly a Bell's palsy, as, in view of the chronic otitis media, it is very probable that the facial nerve was involved as the result of the inflammatory process in the ear.) Twelve years previously she had had an attack of facial paralysis on the right side. She recovered from this seizure completely and showed no evidence of it at her last visit.

CASE 19.—(B.H. No. 65382.) G. W., male, aged 36, following a cold, developed a left facial palsy. This recovered completely in a few weeks. In March, 1928, he had an attack of facial weakness on the right side of his face, associated with tinnitus in his right ear. The facial paralysis cleared up in August, 1928. However, he has been deaf in the right ear since the attack. It is of interest that his blood Wassermann test was 4+. He shows no other evidence of lues of the central nervous system or of more important clinical bearing and presents no other angle or systemic signs or symptoms at this time.

TABLE 1.—SUMMARY OF DATA OF CASES OF RECURRENT FACIAL PARALYSIS.

Case No.	Patient.	Sex.	Age.	Side and times affected.		Interval between attacks.
				R.	L.	
1 . .	L. C.	F	18	1	1	2 mos.
2 . .	A. Q.	F	11	1	1	3 wks.
3 . .	G. B.	F	42	1	1	10 mos.
4 . .	F. H.	M	28	1	1	3 yrs.
5 . .	S. O.	M	32	1	1	6 wks.
6 . .	M. G.	F	25	..	2	7 yrs.
7 . .	W. L.	M	50	2	..	4 yrs.
8 . .	L. T.	F	18	2	..	8 yrs.
9 . .	S. O.	M	20	..	2	2 yrs.
10 . .	M. I.	M	23	..	2	6 yrs.
11 . .	E. S.	M	35	2	..	9 yrs.
12 . .	M. Z.	M	63	..	2	30 yrs.
13 . .	J. C.	F	21	1	1	6 yrs.
14 . .	R. F.	F	23	1	2	8 and 3 yrs.
15 . .	G. R.	M	84	2	..	30 yrs.
16 . .	P. C.	M	56	..	1	12 yrs. (diabetes, Talma operation).
17 . .	A. L.	F	60	1	2	3 and 2 yrs. (diabetic).
18 . .	C. O.	F	29	1	1	12 yrs. (first, Bell's; second, mastoid).
19 . .	G. W.	M	36	1	1	Wassermann, 4 +; deafness, N. on R.

**Discussion.** An analysis of Table 1 causes certain factors to stand out:

Age is no bar to a recurrent facial paralysis. The youngest patient was 11 years, the oldest 84.

The sex incidence was fairly even: 9 females to 10 males.

The intervals between attacks varied between 3 weeks to 30 years.

The possibility of the attack occurring on the opposite side or recurring on the same side is just about even, there being 8 cases with both sides involved and 8 cases with the same side involved. There were 2 patients with 3 distinct attacks in both of which 2 of the 3 attacks recurred on the left side.

Of a total of 293 cases of peripheral facial paralysis treated and examined by the author personally, the paralysis occurred again 19 times (6.4%) from all causes.

The so-called idiopathic, "rheumatic" or "Bell's palsy" occurred again 15 times in 192 cases (7.7%).

Obviously the most common cause of recurrence, as well as the most common cause of paralysis, is Fallopian neuritis or Bell's palsy.



**Summary.** Nineteen patients with a story of recurring attacks of facial paralysis have been considered. Five of these patients were observed in both of their attacks. The remaining 14 cases gave a reliable history in most cases unsolicited of a previous occurrence.

Just as singly the seventh cranial nerve is the most commonly paralyzed nerve in the body, it is also subject most frequently to recurring attacks.

The frequency is 6.4% from all causes, or 7.7% in cases of a Fallopian neuritis or pure Bell's palsy.

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### **PATHOLOGIC PHYSIOLOGY OF THE NEUROGLANDULAR SYSTEM.\***

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WE have been prone to consider that each gland acts independently of all the other glands as well as independently of the nervous system. Not only are there students of individual organs, but there are even students of parts of an organ. Thus there are students of the cortex and students of the medulla of the adrenal glands, of the sympathetic system exclusively and of the brain exclusively. Great progress has been made by these investigators, but many are still apt to think of each gland and of the several parts of the entire nervous system as each endowed with a power of independent initiative and action. It would appear that the time has come when we may put out of our minds the concept that any unit of the great energy system of the organism has inherent initiative.

The organism is normally driven adaptively, that is, only within the range of such activity as is to the advantage of the organism. However, when the various mechanisms of the body, brain, glands, muscles, etc., become so facilitated that they become active beyond

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the bounds of adaptive and beneficial work, the activity being qualitatively normal but quantitatively abnormal, then we may say that a state of pathologic physiology is established.

When the brain, thyroid and adrenal-sympathetic system are in a state of pathologic physiology, the entire organism is speeded even to destruction and death. When the automatic, self-energizing switchboard and the thyroid and the adrenal glands are equally speeded, hyperthyroidism results; but hyperthyroidism is a misnomer, the term *hyperkineticism* is more exact.

Instead of a pathologic physiology of the entire mechanism, there may be a pathologic physiology of one or of a group of glands, or organs or of the nervous system. The thyroid gland cannot of itself initiate a hyperplasia any more than a motor car can start itself; yet the thyroid gland "comprehends" when it is winter, for it enlarges during the winter. It "comprehends" when the mating season comes, for it enlarges during the mating season; it "comprehends" that some part of the organism has tuberculosis, for it becomes enlarged during tuberculosis. The adrenal glands, likewise, enlarge and become active in winter, in the mating season and in the presence of infection.

When a zebra sees a lion, the brain is the switchboard which throws this switch and closes that switch, passing the impulses to certain muscles, inhibiting others, sending impulses to the thyroid and to the adrenal-sympathetic system, inhibiting the impulses that normally go to the procreative organs, the digestive organs and all that part of the body that will not participate in the action that is about to take place. We have become familiar with the great output of adrenalin and the profound stimulation of the thyroid gland, the sympathetic system and the brain that occurs during the sudden get-away of the zebra. The brain has no power within itself to speed up, but it is speeded up by the adrenal and thyroid hormones. The brain is like a flame glowing all the time and, like any other flame, it flares up under accelerators of oxidation. Thus the sight, smell or sound of one animal may act powerfully on the thyroid-adrenal-sympathetic system of another animal. There is no break in the continuity between the thyroid-adrenal-sympathetic system of the zebra and the thyroid-adrenal-sympathetic system of the lion.

If there is a widespread stimulation of the neuroglandular system, that form of pathologic physiology which we call neurocirculatory asthenia may result. If the excessive stimulation of the sympathetic nervous system involves the pylorus with resultant sphincterismus, that form of pathologic physiology which we call peptic ulcer may be produced; if it involves the intestines, that form of pathologic physiology which we call spastic constipation may result. If the disturbance of the function of the pancreas continues, that form of pathologic physiology which we call diabetes may

result. If the continued activation affects several glands—the pituitary, the thyroid, the adrenals, the pancreas, the gonads, that form of pathologic physiology which we call polyglandular disease results.

These diseases which result from a pathologic physiology of the neuroglandular system are peculiar to civilized man. Hyperthyroidism, neurocirculatory asthenia, peptic ulcer, diabetes, polyglandular disease do not appear in animals in the wild state and rarely in domesticated animals. They are exceedingly rare in primitive man and are uncommon in the lower ranks of civilization. The more highly civilized man becomes, the more prevalent do these diseases become.

We have spoken of the pathologic physiology of the brain-thyroid-adrenal-sympathetic system as the result of *continued* activation or stimulation. Pathologic physiology of this system may likewise be the result of repeated stimulations, that is, there may be a training or education in pathologic physiology. In a man or woman who is predisposed by heredity and temperament to excessive fears, worries and strivings, or who, though normally poised, is excessively driven by misfortune, permanent changes may be wrought. Just as by repeated repetition in school the action patterns of the school-boy's brain are created and subjected to a specific facilitation by his teacher in his training and education, just as repeated painful injuries facilitate pain, just as agreeable or disagreeable personalities facilitate attraction or repulsion, just as repetition produces habits, discontents and familiarities, so repeated activations in the neuroglandular mechanism cause such excessive facilitation that *normal* stimuli produce *abnormal* reactions. In other words, there may be a process of training and education in pathologic physiology analogous to training and education in Latin and mathematics.

Not only may the nervous system be facilitated or educated to disease as well as to health, but the nerve pathways, ganglia and synaptic junctions also presumably may be facilitated for either good or evil, and under pathologic stimulation the cellular structure of the thyroid gland may grow in actual size and thereby secure for itself an increased capacity for work. That is to say, we may think of chemical training or education by repeated stimulation, no less than of physical training or education by repeated stimulation.

In some such manner an hereditary predisposition played upon by adverse factors in the environment or in a normal individual under excessive strain, in one case may be looked upon as producing hyperthyroidism, in another as pathologically sensitizing the adrenal-sympathetic system, in another as "stepping-up" the brain to its breakdown, or so facilitating the digestive mechanism in its activations and its inhibitions as to cause spastic colitis, hyperacidity, peptic ulcer or indigestion. In some individuals, the glucose mobilization mechanism may become so affected that diabetes

appears, while in others the sympathetic ganglia become so facilitated, so trained, that the resulting excessive flow of action currents to the walls of the bloodvessels of the extremities leads, for instance, to Raynaud's disease.

These diseases seem to be largely due to hyperactivity of the group of organs that initiate and continue the transformation of energy. Therefore, diseases which are due to pathologic education or facilitation and exhaustion may be termed kinetic diseases.

If our reasoning is correct, and if our premises are established, then neurocirculatory asthenia, hyperthyroidism, peptic ulcer and diabetes belong to the group of so-called kinetic diseases—where there has been bred a sustained, abnormally high activity of the entire brain-adrenal-sympathetic system. The pathologic, emotional states leading up to hyperthyroidism, neurocirculatory asthenia or peptic ulcer may be regarded as similar to "fixed ideas" which produce a pathologic activation of one or more parts of the neuroglandular system.

Just as pathologic education or facilitation may lead to one or another of these kinetic diseases, so education and training may prevent or in certain cases may even cure these diseases. In too many cases, however, the pathologic physiology is so established that training and education must be aided by mechanical interferences with the facilitated mechanisms. Thus a mild case of hyperthyroidism may be cured by a sufficient period of rest; a peptic ulcer may be quieted by rest and diversion. But a return to the customary—too often abnormal—activities of life is almost certain to result in recurrence.

We have, therefore, applied the decisive test of the clinic to our conception of these kinetic diseases by lessening the power of the adrenal-sympathetic system. To this end we have performed 350 operations on the adrenal glands (53 adrenalectomies and 297 denervations).

It should be emphasized that, in the presence of psychoses, neurasthenia, or any condition in which the seat of disturbance is in the brain, adrenal denervation is contraindicated. These are not kinetic diseases and the adrenal-sympathetic system is not involved.

Since epilepsy involves rhythmic hyperactivity of the entire energy system—nervous system, muscular system and glandular system, and since the execution of such a body-wide activity involves the glands that govern energy as well as the brain and nerve ganglia, one might expect that denervation of the adrenal glands and the excision of nerve ganglia might mitigate the severity of the attacks; might convert a major into a minor epilepsy, and possibly might even effect a cure. Even if it were possible only to convert attacks of grand mal into those of petit mal, it would be well worth while. We have treated 46 cases of epilepsy by various types of dekineticizing procedures, 29 by denervation. Sixty per

cent have shown improvement or cure, while in 7 cases the operation has been performed too recently for any judgment as to the results.

Our total series includes 129 cases of neurocirculatory asthenia with improvement or cure in 93% of the uncomplicated cases; 84 of hyperthyroidism with cure in 100%; 40 of peptic ulcer with improvement or cure in 96%; and 11 cases of diabetes. In all of the cases of diabetes, hyperthyroidism was present also and as one would expect, with the cure of the hyperthyroidism the diabetes was ameliorated or cured.

In 9 cases of polyglandular disease or endocrine imbalance manifested especially by hirsutism and obesity, denervation has been followed by disappearance of the hypertrichosis and restoration of a normal habitus.

**Summary.** We have proposed a pathologic functional state of the brain-thyroid-adrenal-sympathetic system as the primary cause of a group of diseases occurring especially in civilized man. We have drawn attention to the energy characteristics that distinguish man. We have emphasized the fact that the brain and the sympathetic nervous system and the glands are indissolubly linked together in function; that the one component of the neuroglandular system that can be normally and pathologically conditioned is nerve tissue, that is, the brain and sympathetic nervous system; that the glands cannot be so conditioned; that the brain and the sympathetic system can be conditioned only with the collaboration of certain hormones and that in the case of civilized man the rise especially of the thyroid gland has so facilitated the conditioning of the brain that man owes his distinctions and his diseases to this unique collaboration. In support of this conception, there are offered the clinical results of the application of this principle in 350 cases of hyperkinetic diseases improved by dekineticizing procedures.

## BOOK REVIEWS AND NOTICES

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CONCEPTION PERIOD OF WOMEN. By DR. KYUSAKU OGINO, Head of the Gynecological Section of Takeyama Hospital, Niigata, Japan (Nippon). English Translation by Dr. YONEZ MIYAGAWA, Director of Government Institute for Infectious Diseases, Tokyo Imperial University, Hongooku, Tokyo, Japan. Pp. 94; 22 tables. Harrisburg: Medical Arts Publishing Company, 1934. Price, \$1.00.

THE Thesis: Ovulation time is from the 16th to the 13th day before the next coming menstruation, and the life duration of the ovum not fertilized is less than two days. Spermatozoa in the uterus and tubes retain for not over three days their ability to fertilize an ovum. The period of possible conception for women is therefore within the 8 days from the 19th to the 12th before the oncoming menstruation, whatever the length of the menstrual cycle. Exceptions to these findings are so rare as to be unimportant in practical life.

Comment: The author is very sure of these conclusions, presents them in convincing manner, with much scientific data, and a considerable mass of human record material. The author and the publisher claim an altruistic attitude toward a needy public. The Rhythm, by Latz, and The Sterile Period in Family Life, by Coucke and Walsh are other attempts to present for practical use this physiology worked out by Ogino, and by Knaus of Austria. Dr. A. G. Miller of Hobart, Indiana, accepts this thesis, and is quoted at length in this book.

If the theory proves to be fact, curiously delayed in coming to light, we predict great advantage from its application. If it proves too good to be true, and does not work in practice, hopeful multitudes will be disillusioned if not desperate. Other published medical evidence, notably a series of 1432 dated conceptions collected by Dickinson & Bryant, show a high fertility during the 5 to 7 days just after menstruation but before Ogino's 8 fertile days in midmonth. This would be explained by longer life for the sperm cell than Ogino has found. There is general agreement among all students of fertility on the existence of a practically sterile period for the 9 to 11 days after ovulation and before the next menstruation. But there appear to be few American physicians willing yet to advise patients to trust a safe week just following menstruation.

L. D.

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AMEBIASIS AND AMEBIC DYSENTERY. By CHARLES F. CRAIG, M.D., M.A. (HON., YALE), F.A.C.P., F.A.C.S., Colonel, United States Army, Retired, D.S.M., Professor of Tropical Medicine, and Head of the Department of Tropical Medicine, School of Medicine, Tulane University of Louisiana, New Orleans, etc. Pp. 315; 54 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$5.00.

THE book opens with an introductory chapter which includes a brief history of the disease, and the parasite, and the present geographic distribution. Then follow, in the order listed, sections on Etiology, including discussion of the morphology and life cycle of the parasite, on Epidemiology, Pathology, Symptomatology, Complications and on Diagnosis; the last named containing extended consideration of complement-fixation tests and culture media. Prognosis, Prophylaxis and Treatment are discussed in

two final chapters. Papers to which reference is made are listed at the end of each chapter. Authors and Subjects are indexed separately. In general, illustrations are well chosen; but several which are intended to show tissue reactions and others of stained ameba are of little value. Also, available material does not entirely support the opinion that *Endamoeba histolytica* is an obligate tissue parasite; nor does the acknowledged efficacy of amebicidal drugs allow treatment to proven cure of all who are infected. On the whole, however, the book is a reasonably complete and up-to-date discussion of a subject which probably has attracted more attention recently than it deserves.

H. R.

**THE RADIOLOGY OF BONES AND JOINTS.** By JAMES F. BRAILSFORD, M.D. (B'HAM), M.R.C.S. (ENG.), Radiological Demonstrator in Living Anatomy, The University of Birmingham; etc. Pp. 500; 310 illustrations. Baltimore: William Wood & Co., 1934. Price, \$9.00.

IN this volume the author gives a comprehensive survey of the radiology of the bones and joints. Each regional portion of the skeleton is considered individually. Reference is made to the ossification, the normal anatomy and anomalous development of the part, in addition to a description of the numerous pathologic processes to be encountered. A few pertinent facts regarding roentgenologic technique are also included. References to the literature are quite numerous and a long bibliography is given at the end of the book. The text is amply illustrated by reproductions of roentgenograms of excellent quality.

The subject matter is well presented, clear, concise and quite complete as regards the many pathologic conditions which may affect the human skeleton. However, the attempt to deal with a subject of such vast proportions in a single volume has made the reference to the individual disease, of necessity, very brief and at times too sketchy to be of real value. As a quick and ready reference for the busy radiologist in his daily contact with diseases of the bones and joints, this work will find its greatest mission.

K. K.

**THE PATIENT AND THE WEATHER. VOLUME III. MENTAL AND NERVOUS DISEASES.** By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 375, lithographed; 192 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934. Price, \$5.00.

THIS, the third of a series of volumes on the relation of the weather to disease, presents the neuropsychiatric viewpoint and gives detailed observations for the use of investigators.

Part I. Interesting chapters are devoted to Focal Reaction in the Psychoses; Oxidation; Malformations; Mental Superiority, Insanity and Inferiority; Seasonal Conception and Suicide. Part II. Psychiatric Episodes and the Meteorological Background; Interrelation of Clinical Status, Blood Chemistry and Meteorological Environment of Eighteen Psychiatric Patients. Part III. Multiple Sclerosis; Tabes and Paresis; Poliomyelitis and Meningitis.

As delineated by these authors, the effects of meteorologic conditions may possibly be so far-reaching as to affect the ovum before fertilization and thus bear upon the future stability of the individual. A fling is taken at psychoanalysis: "In that illuminating study 'Leonardo da Vinci' Freud builds up his entire thesis on a dream of the *infant* Leonardo—a dream which Leonardo may never have had!"

Some of the subject-matter is controversial, but the research is stimulating and should prove useful.

N. Y.

KREBS IM LICHTE BIOLOGISCHER UND VERGLEICHEND ANATOMISCHER FORSCHUNG. By MED. DR. JOS. LARTSCHNEIDER, Linz a. d. Donau. Volume 2, No. 1, Albuminoide, Schilddrüse, Kropf, Hypophyse, Eierstock, Adenosis. Pp. 94; 19 illustrations. Leipzig: Franz Deuticke, 1934. Price, Rm. 5.

This is the second pamphlet of a series, which under an appealing general title assails such doctrines as the Cell Theory, "*omnis cellula e cellula*" and so on in an unconvincing manner, aggravated by obscurities of thought, style and arrangement of material. A characteristic sentence will illustrate: the anterior lobe of the hypophysis "ist eine Drüse vom Typus des menschlichen Eierstockes, bestehend, wie dieser, aus lauter in gemeinsames, von geräumigen Capillaren durchzogenes Stroma gebetteten, nicht epithelial ausgekleideten, den Pflüger'schen Eierstockschläuchen ähnlichen Schläuchen." The illustrations, poorly reproduced from standard texts, constitute the best part of the book. E. K.

MENTAL HEALTH: PAST, PRESENT AND FUTURE. By ARTHUR HILER RUGGLES, M.D., Superintendent of Butler Hospital, Providence, R. I. Pp. 104. Baltimore: The Williams & Wilkins Company, 1934. Price \$1.50.

This addition to the literature on Mental Hygiene tells the need of public enlightenment and of greater concerted effort among workers, if we are to stem the rising tide of mental inadequacy. Statistics have been avoided and this is well for they may, unwittingly, prove deceptive. Just to mention two of several possible errors: formerly, many unfit died through neglect; today, every nook and corner is searched and all sorts of individuals who previously escaped statistical scrutiny now swell the list of the inadequate. Surely, an absolute increase is shown, but that we have a great relative increase is doubtful. Nietzsche said this civilization would end in madness and set the example himself. Of courses the situation is bad—it always has been. But despite the deficiencies of our jungle-forebears, we are here today. N. Y.

PRACTICAL TALKS ON HEART DISEASE. By GEORGE L. CARLISLE, M.D., Associate Professor of Clinical Medicine, Baylor University, Dallas, Texas. Pp. 153. Springfield, Ill.: Charles C Thomas, 1934. Price, \$2.00.

EVERY practitioner of Medicine should have this book in his library: it is essentially practical and written in the intimate manner which makes Sir James Mackenzie's and Sir Thomas Lewis' books so interesting. There is none of the confusing multitude of references which, unfortunately, fill most medical publications in this country. The order in which the subjects are presented may be criticized, as it would seem wise to follow the Nomenclature approved by the American Heart Association, namely, to present Cardiovascular Disease in the order of Etiological Factors (Congenital Developmental Defects, Rheumatic Fever, Syphilis, Hypertension, Arteriosclerosis, etc.). Carlisle makes the sound statement that "*It takes time to take a history, but it is the most important point in examining a patient for any disease, and the heart case is no exception.*" Reference to venous engorgement of the cervical vessels is omitted in the first chapter, but mentioned in the second. The author locates the apex beat and left cardiac border from the nipple line in man, and the midclavicular line in women; it is more customary to locate it in centimeters from the midsternal line. I do not agree with the author that percussion of the cardiac diameters is a waste of time; but I certainly agree that considerable time should be spent on arriving at an average blood pressure, rather than merely making one



observation. His statement may be questioned that "A thrill always means an abnormal heart but not by any means a serious heart affliction." The summary of our knowledge of hypertensive heart disease with suggestions as to treatment, is practical and well presented. His admittedly personal enthusiasm for Small's serum and antigen of "*Streptococcus cardio-arthritis*" in the treatment of rheumatic fever is not shared by most cardiologists. He says "The systolic pressure may be 200 or more and the diastolic 20, 30 or even down to zero." Certainly a diastolic pressure of zero is not compatible with life; if the diastolic pressure is determined by the fourth phase, diastolic pressure will seldom be found below 20. It is astounding that, in an otherwise accurate book, there should be the apparent confusion in the differential diagnosis between acute rheumatic heart disease and subacute infective endocarditis. The author has described embolic phenomena with an enlarged spleen and red cells in the urine in acute rheumatic heart disease; of course these are diagnostic phenomena in subacute infective endocarditis. His chapter on Premature Contractions or "Extrasystoles" is a masterpiece. The consideration of Angina Pectoris might be criticized for omitting a more definite differential diagnosis between angina of effort and coronary occlusion. Under Treatment in Coronary Obstruction, no mention is made of an oxygen tent or chamber. The chapter on Cardiac Neurosis shows balance and good judgment, the book ending with the sentence "Intense fear of heart disease is more distressing than most real heart disease." In summary, this book must be classified in American medical literature as one of the major contributions on the subject of cardiovascular disease. W. S.

FIFTY YEARS OF MEDICINE AND SURGERY. An Autobiographical Sketch. By DR. FRANKLIN H. MARTIN. Forewords by WILLIAM J. MAYO, M.D., Rochester, Minn., and GEORGE W. CRILE, Cleveland, Ohio. Pp. 449; illustrated. Chicago: Surgical Publishing Company, 1934. Price not given.

"A CONSTRUCTIVE dreamer" and "one of the most distinguished of American surgeons," as he is called by G. W. Crile and W. J. Mayo in the two Forewords, Franklin Martin should have interesting things to tell us. His two major achievements, the creation of a great medical journal "*Surgery, Gynecology and Obstetrics*" and the founding of the American College of Surgeons, are covered in 6 and 102 pages respectively; yet the description of the tribulations and success of the College—history in the making—is none too long. Nor will it be as interesting to most readers as the earlier parts of these reminiscences, telling in a simple, artless and entertaining style the professional and personal life of a rising young Chicagoan. For the author's first 30 years one must turn to the first 10 chapters of his other autobiography, "*The Joy of Living*." E. K.

HORMONE UND INNERE SEKRETION. (Band 19 of Wissenschaftliche Forschungsberichte Naturwissenschaftliche Reihe, Herausgegeben von Dr. Raphael Ed. Liesegang, Frankfurt a. M.) By DR. FRITZ LAQUER, Wuppertal-Elberfeld Professor an der Universität Frankfurt. Pp. 368. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 18.

In the 6½ years that have elapsed since the first edition of this summary of the endocrine situation, the author has examined ten thousand new articles of which over six thousand have been "noticed"! For insulin alone 1245 references are given, and the thyroid, parathyroid, adrenals, hypoph-

ysis and gonads get equally generous treatment. The thymus and pineal, circulatory and intestinal hormones, and those of hypothetical nature, receive consideration in a final chapter. While such an approach necessarily produces a summary style that discourages consecutive reading, it has produced a useful guide through a devious field and a very valuable book of reference. E. K.

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VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Seventh Session. By PROFESSOR DR. EB. KOCH, Bad Nauheim. Pp. 326; 65 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 15.

AMONG the numerous articles, chiefly on thrombosis and embolism—the topic to which this session was devoted—those by Aschoff, Dietrich and Morawitz are pre-eminent. For Aschoff, thrombosis is not due to a single cause, but rather a function of a number of variables chiefly of a physical nature. Important are the number and agglutinability of the platelets and such humoral factors as the blood velocity. For Dietrich, the relations of the blood to the vessel wall, as brought out by endothelial sensitization experiments, is of prime importance. Morawitz, from an eclectic clinical viewpoint, accepts blood and vessel wall changes of toxic, infectious and allergic nature, but emphasizes the nutritional factor. For his capillary thrombometer he claims the important ability to estimate the tendency to thrombosis from examination of blood samples. E. K.

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ERBPATHOLOGIE, EIN LEHRBUCH FÜR ÄRZTE. (Band 18 of Medizinische Praxis, Sammlung für Ärztliche Fortbildung. Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme, Prof. Dr. K. Warnekros.) By DR. O. FREIHERR VON VERSCHUER, Ausserordentlicher Professor der Universität Berlin und Abteilungsleiter am Kaiser-Wilhelm-Institut für Anthropologie, menschliche Erblehre und Eugenik, Berlin-Dahlem. Pp. 213; 32 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 8.

THIS 18th volume of a series devoted to practical postgraduate medical education tackles a difficult subject. To bridge the gap between the scientific and practical aspects of heredity in disease, the first half of the book gives a none-too-clear exposition of Mendelism, Mutations, Constitution and Race-pathology. In the second half is found an alphabetical list of diseases in which heredity may play a part. So many are included that often they have to be dismissed with some such statement as: "Athetosis has been observed in families." A final section of 40 pages endeavors to apply Erbpathologie to the etiology, pathogenesis and treatment of disease. E. K.

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THE SPASTIC CHILD. A Record of Successfully Achieved Muscle Control in Little's Disease. By MARGUERITE K. FISCHEL. Pp. 97; 2 illustrations and 14 figures. St. Louis: The C. V. Mosby Company, 1934. Price, \$1.50.

THE author of this book for lay readers describes her methods, many of them self-devised, for combating the various manifestations of Little's disease in her son from his infancy to his sixteenth year. The special training program included physical, educational, and psychological approaches. The text is biographical and is intimately individualized. Although the necessity for courage and patience is quite properly emphasized,

many generalizations drawn by the author are hardly acceptable. Some of her methods, indeed, would be ineffectual or even harmful if applied indiscriminately in more severely affected cases of Little's disease or in spastic afflictions whose courses are progressive rather than stationary or regressive. The book should offer hope and encouragement to parents, but as a technical guide to the management of spastic children generally it is not to be recommended.

M. C.

**MANUAL OF CLINICAL LABORATORY METHODS.** By PAULINE S. DIMMITT, Ph.G., Medical Technologist for the Stout Clinic, Sherman, Texas, etc. Pp. 156; 36 illustrations, including 7 colored plates. Philadelphia: F. A. Davis Company, 1934. Price, \$2.00.

This little manual presents the usual technical steps employed in a hospital laboratory, including the *Van den Bergh* tests, the icteric index and *Hydatidiform Mole* and *chorionepithelioma*.

While brevity is always desirable the subject matter in this manual seems to have been too briefly considered. For example, the whole discussion on human parasites is in four sentences. Often only a single procedure is outlined for an important examination and here the choice of test may be questioned by many. An example of this is the selection of a drop method (watch-glass and glass bead) for determining the coagulation time of blood.

Only the steps in performing the various tests are given. The sources of error are not discussed and reasons for important steps are omitted. To use this manual one should already have an excellent knowledge of the subject matter to adjust an error or overcome other difficulties that a technician very often meets.

J. B.

**SYNOPSIS OF GENITOURINARY DISEASES.** By AUSTIN I. DODSON, M.D., F.A.C.S., Professor of Genitourinary Surgery and Genitourinary Surgeon to the Hospital Division, Medical College of Virginia. Pp. 275; 111 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, \$3.00.

A most exceptionally complete, accurate and safe compendium of the entire field of urology. Its 14 chapters are equally thorough, though brief, and present in each instance modern thought on etiology, pathology, diagnosis and treatment. It is essentially a student's guide and a handy reference to the diagnostic methods with which the physician in practice should be familiar.

A. R.

**CLINICAL PATHOLOGY OF THE JAWS.** By KURT H. THOMA, D.M.D., Charles A. Brackett Professor of Oral Pathology in Harvard University; Oral Surgeon to the Brooks Hospital, etc. Pp. 643; 423 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$9.00.

The endeavor of the author "has been to produce a complete work, including all malformations, diseases, and neoplasms of the jaw." It was designed as a textbook for students as well as a reference book for investigators and practitioners. Illustrations are numerous; the photomicrographs excellent. Some of the reproductions of gross specimens, which are less satisfactory should be omitted or improved in a second edition. In their present form they are of little aid in recognizing the condition described.

The clinical aspects are made more realistic by the inclusion of case histories, following the lead of Cabot and Morat (*Einführung in die Klinik*

der Zahn- u. Mundkrankheiten, Leipzig, 1920). The manner in which the subject matter is treated will go far toward demonstrating the indispensability of pathology in surgery. Thoma's experience in surgery and interest in pathology warrant that careful attention be given to his opinion. Most of the conditions described are either never or very rarely seen by the general practitioner of dentistry. If occasionally he feels oppressed by the monotony of his work, he will be refreshed by spending a few half-hours over this work which deals with a related if somewhat novel field.

The Reviewer is curious about two omissions. In the chapter dealing with fractures of the jaws, no consideration is given to the recent monograph by Ivy and Curtis (Fractures of the Jaws, 1931, Lea & Febiger, Phila.). Likewise it is hard to understand how Dorrance's views (Operative Story of Cleft Palate, 1933, Saunders, Phila.) can be completely disregarded in any discussion of cleft palate and harelip.

Typography and general physical make-up are in every respect admirable.  
J. A., Jr.

GRACIAN'S MANUAL. By DR. MARTIN FISCHER, Professor in the University of Cincinnati. Pp. 305; 2 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$3.00.

DR. FISCHER's translation of these much translated aphorisms has the merit, mostly lacking in other translations, of going back to the original text. Its "clipped" apostrophic style and content, well preserved in the translation, may be illustrated by such excerpts as: "Do not be a scandal sheet. Much less be esteemed one." In evaluation, to follow the golden mean that Gracian recommends, these aphorisms may be regarded as characteristically Jesuitical, expressing a number of high ideals as well as sound truths, many of which we are slow to admit publicly even in the nineteen thirties.  
E. K.

RESEARCHES IN CANCER: PART I (1896-1921: 1922-1932). By CALEB WYAND GEETING ROHRER, B.Sc., Shenandoah College, Va.; M.D., College of Physician and Surgeons of Baltimore, Md.; M.A. and Ph.D., Illinois Wesleyan University, Ill. Pp. 144; 22 illustrations. Baltimore: The Brentwood Printing Co., 1934. Price, \$5.00.

HAVING survived "repeated rejections by astute editorial boards," the essays that compose this book have now been privately printed. They elucidate the author's theory of cancer, *i. e.*, that premature birth, the primary cause of cancer, is responsible for the groups of immature cells which, in line with Cohnheim's theory, develop into either benign or malignant neoplasms. An increased supply of oxyhemoglobin to these "fetal imperfections" is regarded as the exciting cause. On this basis, the author believes that he has obtained good results in treating 13 cancer cases with a glycerinated suspension of fetal tissue. No evidence is included to support his views.  
E. K.

DIABETIC MANUAL FOR PATIENTS. By HENRY J. JOHN, M.A., M.D., F.A.C.P., MAJ. M.R.C., Director of the Diabetic Department and Laboratories of the Cleveland Clinic. Pp. 232; 47 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1934. Price, \$2.00.

In this edition the diet lists have been fully revised using protein, fat and carbohydrate in the proportions commonly prescribed today. Fewer diets are listed in greater variety. Chapters have been added on Marriage and Summer Camps for Diabetic Children. The feature of the book continues to be a clear presentation of the disease and its management which should encourage the intelligent diabetic.  
F. L.

## NEW BOOKS.

- The Advance of Science.* Edited by WATSON DAVIS, Director, Science Service, Washington. Pp. 400; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1934. Price, \$3.50.
- The Constitution and Its Reaction in Health.* By T. E. HAMMOND, F.R.C.S., Assistant Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 160. London: H. K. Lewis & Co., Ltd., 1934. Price, 7/6.
- Gracian's Manual.* By DR. MARTIN FISCHER, Professor in the University of Cincinnati. Pp. 305; 2 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, \$3.00. (Review, p. 287.)
- Treatment by Diet.* By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago; Formerly Consulting Physician, The Mayo Clinic. Pp. 615; illustrated. Philadelphia: J. B. Lippincott Company, 1934. Price, \$5.00.
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## NEW EDITIONS.

*Surgical Applied Anatomy.* By SIR FREDERICK TREVES, BART. Pp. 720; 174 illustrations, including 66 in color. Ninth edition revised by C. C. CHOYCE, C.M.G., C.B.E., B.Sc. (N.Z.), M.D. (EDIN.), F.R.C.S. (ENG.), Professor of Surgery, University of London; Director of the Surgical Unit, University College Hospital Medical School, etc. Philadelphia: Lea & Febiger, 1934. Price, \$4.00.

This ninth edition continues as one of the most useful compendiums on an essential subject, the text having been brought up to date by Professor Choyce. The surgical anatomy is discussed according to the various regions of the body: diagrammatic and schematic drawings illustrating the essential facts. L. F.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF  
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### ACUTE APPENDICITIS.

For the last decade there has been a renewed interest in the subject of acute appendicitis and during the past year a number of very interesting papers have appeared on this subject. It is realized that both the incidence and mortality are increasing and that there is a wide disparity in the results of treatment in certain large medical centers and in the country as a whole.

From the time that Mestivier<sup>1</sup> of France, in 1759, demonstrated by autopsy the first recorded case of disease of the appendix to within 25 years of the appearance of Reginald Fitz's<sup>2</sup> paper in 1886, there was a total of 141 cases of this disease recorded in medical literature. The Willard Parker<sup>3</sup> procedure, first advocated in 1867, consisted solely of incision and drainage for appendiceal abscess. Kelly<sup>4</sup> states that "To Thomas G. Morton of Philadelphia belongs the credit for the first successful operation for the removal of the appendix, deliberately undertaken." The date was April 27, 1887.

John B. Deaver<sup>5</sup> has very clearly outlined the early history of this subject in this country. He referred to the differences of opinion which existed in regard to the treatment of appendicitis as follows: "Not only was the controversy as to the surgical or non-surgical treatment of appendicitis the occasion for unpleasant personalities, that were as galling as they were undignified and unjust, but it was the cause of bitter enmities that often persisted during a whole lifetime. From the beginning of my recognition of the importance of the potential mischief resident in the appendix, I was one of the ardent advocates for its removal in acute cases of inflammatory disease of the organ, and later on also for its routine removal in many diseases of other abdominal viscera. Arrayed with me on the affirmative side of the question were men like Morton, Pepper, Osler, the two Prices of this city, Maurice Richardson, John Murphy, and others who have passed on to their

reward; and still others, McBurney, Keen, the Mayos, Ochsner, and many more who are happily still keeping alive the good name of surgery in America, and whom I deem it a privilege to count among my friends.

"Prominent among contemporary opponents to early operative treatment of appendicitis was Nicholas Senn, who on one occasion at a meeting of the American Medical Association did me the honor of declaring in public that a surgeon holding the views I was advocating was so questionable an ornament to the profession that he ought to be deprived of his privileges and of his diploma. My answer to his insinuation I am afraid, was about as flattering to my denouncer as was his accusation to me. A few days after Dr. Senn's arrival home he wrote me: 'While we fight like bulls within the arena, behind the scenes we are peaceful lambs; I am very anxious to have you address the Senn Festsschrift Medical Society.' This is by no means an extreme nor an isolated example of the bitterness that marked the stormy controversy at its height. But the atmosphere has been cleared since those days, and the primary question no longer is whether to operate but rather when and perhaps how to operate."

In 1914 the late John B. Murphy<sup>6</sup> stated that the mortality from appendicitis was far too high and one year later Haggard<sup>7</sup> of Nashville agreed with him when he stated that "hospital reports for the past year show that the average mortality in appendicitis in all stages of the disease in those reported hospitals is about 20 per cent." A decade later A. Murat Willis,<sup>8</sup> from a study of vital statistics, called our attention to the increase in the mortality after operations for appendicitis since the Word War. He called attention to a rise in the appendicitis death rate from 11 per 100,000 deaths in 1900 to 14.4 per 100,000 in 1921 and concluded: "Destructive criticism is of small value unless it prepares the way for subsequent improvement. The presentation of facts which has just been made indicates that something is radically wrong with the modern surgical treatment of certain important conditions. Can this be remedied? It would seem that the first step would be the appointment by the American College of Surgeons of a commission, composed of the leading surgical teachers of this country; the function of this commission being to direct a thorough investigation of the whole question, with a view to effecting some degree of standardization of the methods of treatment of these diseases, regarding which, at present, there seems to be such a complete lack of agreement."

In this paper were also reported statistical data from several clinics as follows:

	Death rate percentage.
"Ochsner, Professor of Surgery, University of Illinois, reported in Clin. Surg., 1912, from 1901-1905 . . . . .	4.1
Personal Communication, September, 1924 . . . . .	2.0
Deaver, Professor of Surgery, University of Pennsylvania, reported in Ann. Surg., June, 1924.	
Using method of Gatch, 1901-1905 . . . . .	10.5
Using the Ochsner method, 1910-1919 . . . . .	3.9
Gatch, Professor of Surgery, Indiana University, reported in Ann. Surg., 1924, June, rate for 1924 . . . . .	8.7"

In 1927 the late Ashley P. C. Ashhurst<sup>9</sup> reported on 247 patients on whom he personally had operated and in whom drainage was necessary. The mortality was 13.7%.



Two years later John O. Bower began the first of a series of surveys of the mortality from operations for acute appendicitis in 28 of the larger hospitals of Philadelphia. These surveys have been continued every year since then. During this period there has been an intensive educational campaign on the subject of appendicitis and its complications, in which the Philadelphia Association of Retail Druggists has coöperated. The following table gives the data compiled by Bower<sup>10</sup> over a 6-year period:

ACUTE APPENDICITIS, PHILADELPHIA HOSPITALS (BOWER).

Year.	Number of cases.	Number of deaths.	Per cent mortality.
1928-1929	5121	306	5.97
1930	3095	149	4.81
1931	3142	138	4.39
1932	3546	122	3.44
1933	3783	134	3.54

Bower<sup>10</sup> gives the causes for the increasing mortality as (1) delayed hospitalization, (2) less competent management of spreading peritonitis, (3) increase in the administration of laxatives.

The results of the Philadelphia campaign Bower gives as follows: "The family physician has benefited by the campaign. Unfortunately, the percentage of physicians who follow their patients to the operating room is too small. Early pathologic changes, which can be correlated with symptoms and signs, can be seen in no other way.

"The internes have profited. This is shown by the improvement in clinical records—better histories are usually accompanied by more careful physical examinations.

"The anesthetists play a part in the making of a clinical record which has an indirect bearing on the average case, although they have not been affected directly by the campaign.

"The pathologist, however, has been affected. Fewer cases of peritonitis—fewer deaths from peritonitis.

"The nurses have benefited and they have been excellent propagandists in the spreading of information relative to earlier hospitalization and the dangers of administration of laxatives.

"The surgeons have profited; patients have been admitted earlier—the number of cases of Spreading Peritonitis admitted have been fewer. The following table shows this improvement over a period of 5 years."

RESULTS OF APPENDICITIS CAMPAIGN, PHILADELPHIA 1928 TO 1933.

	1928, %.		1933, %.	
Reduction in Mortality from	5.97	to	3.54	41.0% decrease
Increase in Clean Cases from	57.04	to	73.75	29.5% increase
Decrease in Mortality of				
Spreading Peritonitis from	33.95	to	24.61	27.61% decrease

Although all writers are not in complete agreement with the use of vital statistics as a method of collecting data on the death rate from appendicitis, even Walker<sup>11</sup> who takes exception to some of Willis<sup>12</sup> statements agrees that the mortality is still too high since he states: "We do not wish to avoid the issue that more individuals have died as a result of the endeavor to cure appendicitis during recent years

than previously." It is generally agreed that two important factors contributing to the present high death rate are delay in operation and catharsis.

Acute appendicitis is a surgical disease. There remain then only three factors which may delay operations: (1) failure of the patient to consult his physician; (2) failure of the physician to diagnose the lesion, and (3) procrastination by the physician once the lesion has been diagnosed. Willis<sup>12</sup> has very aptly stated that "provided a good hospital and a capable surgeon are available and a diagnosis of acute appendicitis has been made, prompt operation is the treatment."

The diagnosis of acute appendicitis is not always a simple matter. Too often the physician waits until a textbook picture is present before consulting the surgeon, a time at which perforation may have already occurred. The symptoms will continue to vary as long as the virulence of the infection varies and as long as the quantitative reaction to infection varies in different individuals. Many more patients have been lost as the result of a delay in operating than have been lost from an occasional error in the diagnosis. The surgeon is seldom responsible for this delay.

It may be said that the increase in mortality is associated with an increase in the number of operations for appendicitis. That there has been an increased incidence is without question, for Walker<sup>11</sup> found a rise of 277% in certain districts of New England for the 4-year period 1927 to 1930 over the period of 1907 to 1910. It would appear, therefore, that the disease is being diagnosed with increasing frequency, at least in some sections. If this is true the increase in the mortality rate must be associated with an increase in the number of operations being done by inexperienced and poorly qualified surgeons.

Bower<sup>10</sup> recently suggested "That the surgical service in our hospitals as it pertains to acute appendicitis be modified to the extent that the junior members of the surgical group manage the clean cases but that a consultation be held with the chief of service regarding the management of the perforative or suspected perforated case. Neither a watchful-waiting nor a drastic policy is advocated, but a request that the 12 or 15% of patients admitted to our hospitals with Spreading Peritonitis, who have only one chance in four of living, be given the benefit of all that the service affords in the matter of surgical judgment and experience. Wisdom in surgery usually increases with experience, but not always. The clinical records reviewed showed that a man may spend decades managing Spreading Peritonitis and still have a mortality of 65%. The associate of the surgical service should concentrate on the pre-operative diagnosis of Spreading Peritonitis; his chief should concentrate on management and be willing to pass along to his associates the knowledge he has gained in the managing." The suggestion which Bower made is a good one and if followed closely could not but result in a lower operative mortality.

The mortality of simple acute appendicitis is negligible. As Ashhurst<sup>9</sup> and Shipley and Bailey<sup>13</sup> have said, most deaths occur in the delayed group. Sworn and Fitzgibbon<sup>14</sup> have recently reported the data on 2126 patients with acute appendicitis operated on in St. Thomas' Hospital, London, from 1920 to 1929. There were 231 cases of diffuse peritonitis from appendicitis of 1, 2, 3, or 4 days' duration with a mor-

tality of approximately 19%. Of 487 cases of abscess the mortality was less than 4%, and in 1340 cases without peritonitis the mortality was only 1.71%. These data could be repeated by reviewing the statistics found in any surgical clinic, since there is no disagreement with the statement that delay in hospitalization results in an increase in the number of patients admitted in the various stages of peritonitis.

That the mortality with or without peritonitis can be reduced if careful attention is given to the various details of pre-operative treatment, the judicious selection of anesthesia, the careful planning of the operation and exacting postoperative care is without question.

Many years ago Clark<sup>15</sup> discussed the results obtained in peritonitis after the use of large doses of morphin. Later Ochsner<sup>16</sup> suggested that in the late cases of peritonitis from appendicitis, operation be delayed until the peritonitis was localized. In the interim he suggested fluid by rectal drip, the maintenance of the Fowler position and morphin.

It is agreed that in the early cases early operation is indicated. In the late cases, however, there appears to be no such unanimity of opinion. Tait<sup>17</sup> believed that purgation rather than rest with morphin was indicated in peritonitis. Stockton<sup>18</sup> found the use of morphin helpful, while Bovée<sup>19</sup> in an article published in the same issue of the same journal took the opposite point of view. For years John B. Deaver subscribed to and was one of the most ardent advocates of the Alonzo Clark-Ochsner method of treatment in spreading peritonitis.

The matter has not as yet been finally settled. Even among those surgeons who believe that the delayed method of treatment in spreading peritonitis results in a lower mortality there is no agreement as to the time limit for the immediate and the delayed operation. Thus, Arnheim and Neuhof<sup>20</sup> operate immediately on all patients having a 24-hour history, while after this time they frequently delay operation. And yet rupture with a rapidly spreading peritonitis may occur 2 hours after the onset of symptoms.<sup>21</sup> In a discussion before the Royal Society of London, Ryle<sup>22</sup> favored deferring operation in some of the late cases and immediate operation in others. Rayner<sup>23</sup> delayed operation only long enough to improve the patient's condition, while Morley-Fletcher<sup>24</sup> quoted Sir James Berry as saying that "he deprecated the present practice of operating immediately in all cases of appendicitis. He believed that in acute appendicitis in children immediate operation was indicated. We believe this point of view is well taken, since in children localization does not take place so readily, and it is more difficult with them to withhold fluids by mouth for long periods as is often necessary when the delayed treatment is used. Colley-Davies<sup>25</sup> on the other hand was opposed to a delay in the operation when peritonitis was present which he stated would "put the profession back 20 years in the period of generalized peritonitis, pylephlebitis and subphrenic abscess." Cope<sup>26</sup> believed that delay was often advisable in patients with spreading peritonitis.

Little would be gained by further reviewing the opinions of various writers. The reviewers believe in the delayed treatment in the presence of generalized peritonitis; except in children as above indicated. In such cases the administration of adequate doses of morphin prevents overdistention of the small bowel. It assists in maintaining the tonus of the bowel and by controlling distention prevents disturbances in the

circulation of the intestine. The work of Plant and Miller<sup>27</sup> and of Orr<sup>28</sup> well illustrate these facts. The use of suction drainage, as described by Wangenstein,<sup>29</sup> of the Fowler position and the intravenous administration of sodium chlorid and glucose all aid in permitting the operation to be delayed until such time as localization has occurred.

**Anesthesia.**—Several years ago Foss<sup>30</sup> stated that the mortality after operations for acute appendicitis was reduced 50% since the routine use of spinal anesthesia. Arnheim and Neuho<sup>20</sup> advocate the use of avertin and nitrous oxid and oxygen. They believe that the shock which may result from spinal anesthesia lowers general resistance to infection and thus invites the spread of the infection. There appears to be no basis for the foregoing statement and the reviewers are not in agreement with it.

Rayner<sup>23</sup> favored spinal or nitrous oxid and oxygen rather than ether or chloroform anesthesia. Morley-Fletcher<sup>24</sup> believed spinal anesthesia was superior to general anesthesia. The relaxation afforded by spinal anesthesia permits of operation with a minimum of trauma. The extensive use of gauze packs is not required. Postoperative pulmonary complications are not so frequent and the anesthetic is without effect on the liver parenchyma. In the early cases it should make little difference which anesthetic is used; but in the patients with a diffusing peritonitis, spinal anesthesia would seem to be the anesthetic of choice.

**Incision.**—It is our opinion that the incision suggested many years ago by McBurney is still the best one to use in cases of acute appendicitis. Arnheim and Neuho<sup>20</sup> state that the majority of their patients have been operated on through a rectus splitting incision. The argument used in favor of the rectus incision is that it provides wider exposure; that the use of a routine incision is illogical; that it may make access to the appendix more difficult, and may lead to spread of the infection. These objections we believe to be largely imaginary, since the McBurney incision in the majority of instances provides the most direct access to the appendix, it can be lengthened in any direction and of all the incisions it is least likely to result in a spreading of the infection. The right rectus incision on the other hand provides direct access to the small bowel and thus favors the spread of the infection by carrying an infected focus across small bowel which may as yet be uncontaminated.

Colt and Morrison<sup>31</sup> reported that the mortality in their cases from 1923 to 1929 was 0.69% when the Battle incision was used and 6.05% when the paracentral incision was used. They attributed the higher mortality associated with the paracentral incision to the fact that there was greater possibility of spreading the infection when it was used.

Reid<sup>32</sup> has expressed an opinion in regard to the McBurney incision with which the reviewers are in complete agreement: "The author and the members of our surgical department have long ceased to have a feeling of embarrassment after making a McBurney incision for a mistaken diagnosis of acute appendicitis. With no appreciable reduction in the elapsed interval between the onset of symptoms and operation or in the use of purgatives prior to surgical treatment the death rate for all forms of acute appendicitis treated in the Cincinnati General Hospital has been reduced by 50.3% since the routine of a rectus incision was abruptly and completely changed to that of a McBurney incision." A review of statistical data reveals the important fact that the mortality

from acute appendicitis is lowest in those cities in which the McBurney incision is most widely used.

**Technique.** In 1901 it was suggested by Morris that in appendiceal suppuration the appendix be removed and as much of the pus be aspirated as possible, after which the abdomen be closed without drainage. Buchanan in 1910 and again in 1923<sup>34</sup> has reported favorable results after the use of this method. The procedure has gained more or less favor because of the incidence of intestinal obstruction following drainage of the peritoneum and the knowledge that the general peritoneal cavity cannot be drained.

Shipley and Bailey<sup>13</sup> in a discussion of the treatment of acute appendicitis with peritonitis state that "drainage material, especially in the lower abdomen, often causes widespread adhesions between loops of intestines, mesentery, omentum, pelvic organs and abdominal wall. The drains are soon sealed off and do not drain any considerable portion of the peritoneum." These authors advocate in early peritonitis, removal of the appendix, aspiration of free fluid and exudate and then irrigation of the contaminated area with warm normal salt solution which is then aspirated. After this the peritoneum is closed without drainage. In the discussion of Shipley and Bailey's paper Eugene Pool<sup>35</sup> stated that, "all accept the fact that the wound should be closed without drainage if it is reasonable, but a certain number of cases must be drained. Dr. Shipley makes a great mistake in irrigating within the peritoneal cavity. Blake advocated irrigation many years ago but he has since admitted the fact that it is a mistake."

We do not believe that irrigation is of any value. When practised through the median incision as suggested by Torek<sup>36</sup> considerable trauma to the serous surfaces of the bowel must result. It should be remembered that to a degree fibrinous exudate is protective and that when it is removed there remain behind large areas of denuded gut. Drainage should be practised only when a considerable amount of necrotic material is left behind. When drains are used these should be soft and should be placed along the lateral abdominal or pelvic wall.

In the postoperative period the use of a suction drainage in the presence of peritonitis is a distinct advance in treatment. It has been our experience that since this procedure was instituted postoperative jejunostomy or ileostomy for adhesive obstruction is only rarely indicated.

We have occasionally done an appendicostomy at the time of removal of the appendix in the very sick patient. The method was suggested to us by Wilson of Emporia, Kansas. Recently Jones<sup>37</sup> has reported the use of this procedure in late cases with the most gratifying results. Without doubt it could be used more frequently than it now is.

It is necessary that the surgeon and his staff be ever alert to the complications which may occur during convalescence. Arnheim and Neuhoof<sup>38</sup> have rightly stated that when the patient fails to do well after operation, the surgeon should first look to the abdomen for the cause of the trouble rather than to the chest and more distant areas.

The final solution of the high mortality in acute appendicitis must depend on earlier operation. To attain this there should be an intensive national education campaign among the laity and a closer coöperation between the general practitioner and the surgeon.

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## OPHTHALMOLOGY

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## RETINITIS PIGMENTOSA.

RETINITIS pigmentosa has generally been considered to be a hereditary and familial disease, usually progressive and essentially incurable. Its etiology has not been definitely established. Its outstanding subjective

symptom is night blindness, with loss of central vision a secondary and subsequent feature. Its most prominent objective symptoms are narrowing of the retinal arteries and deposits of pigment in the retina. In most cases it is an isolated lesion. Whether all forms of pigmentary degeneration of the retina of progressive character and unknown etiology should be classified as variants of the typical retinitis pigmentosa is difficult to say. The association, at times, of apparently typical retinitis pigmentosa with nerve deafness, epilepsy, and mental deficiency has long been known. In more recent years the recognition of the Laurence-Biedl syndrome, the finding of pigmentary degeneration of the retina in certain disturbances of hepatic function, the demonstration of hemeralopia as a definite symptom of avitaminosis, and the study of the vasodilating effects of sympathectomy have led to renewed interest in attempts to arrest the progress of typical, isolated retinitis pigmentosa by treatment with various hormones, with diets high in vitamins, with vasodilating drugs, and with cervical and cervicothoracic sympathectomy.

Verhoeff's<sup>1</sup> histologic examination of an eye, which was removed during life and which had been blind with retinitis pigmentosa for more than 20 years, confirmed Leber's<sup>2</sup> opinion that the essential ocular lesion in retinitis pigmentosa is progressive degeneration of the neuroepithelium, the rods being affected first. The changes affecting the pigmented epithelium probably result from degeneration of the neuroepithelium. The choriocapillaris was normal and Verhoeff was of the opinion that obliteration of the choriocapillaris or choroidal circulation can be dismissed as a possible cause of retinitis pigmentosa. In his case there was no definite degeneration of the ganglion cells or atrophy of the optic nerve. The reduction in caliber of the retinal vessels, which is apparent ophthalmoscopically, is seemingly produced by thickening of the connective tissue of the adventitia, without any obvious microscopic reduction in the lumen. As a result of their experiments with the injection of granules of melanin into the vitreous of rabbits, Friedenwald and Chan<sup>3</sup> concluded that all the histologic changes in the retina in retinitis pigmentosa can be accounted for on the hypothesis of a primary lesion of the retinal neuroepithelium, with secondary, long continued infiltration of the retina with melanin granules.

Verhoeff called attention to the possibility that retinitis pigmentosa is the result of disturbance of hepatic function. In certain diseases of the liver, notably hypertrophic cirrhosis, night blindness occurs which possibly is the result of an excess of bile salts in the blood that may affect the visual purple and the rods in which it is supposed to reside. Verhoeff cited the experimental work of Sugita which indicated that the pigmented epithelium and neuroepithelium of the retina can be injured by certain constituents of the bile acting through the blood. He also quoted the investigations of Takahashi, who found the hepatic function abnormal in 12 cases of retinitis pigmentosa. Boenheim,<sup>4</sup> Moreau,<sup>5</sup> and Satanowsky<sup>6</sup> also called attention to the disturbance of hepatic function in certain cases of retinitis pigmentosa.

Collins<sup>7</sup> was of the opinion that retinitis pigmentosa was an abiotrophy of the retinal neuroepithelium, since the rods and cones belong to the class of cells which in adult life lose their power of proliferation and may, in certain cases, die early in life. Verhoeff thought that this

theory explains the facts well but offers no hope for methods of controlling the disease. A study of cases of the Laurence-Biedl syndrome throws a somewhat different light on the possible nature of this abiotrophy.

The association of adiposogenital dystrophy, mental deficiency, retinitis pigmentosa, and polydactylism has been recorded in the literature in from 40 to 50 cases. The recent cases have been grouped under the title Laurence-Biedl syndrome. The cause of this syndrome was originally supposed to be a disturbance of the pituitary gland. Later, Biedl<sup>8</sup> suggested that the essential factor in the production of the syndrome was the presence of an unusually high or massive dorsum sellæ which prevented the passage of pituitary secretion through the stalk to the floor of the third ventricle, as a result of which certain metabolic and genitotropic centers were affected. Ornstein<sup>9</sup> advanced the hypothesis that this syndrome is dependent on a developmental defect of the ectopic zone of the prosencephalon, since, embryologically, the hypothalamus and optic chiasm take origin from the ventral segment and the end brain from the cephalic segment of this zone. This defect results in an abiotrophic condition of the infundibulum, the optic nerves, and the retina, since, according to Tilney and Riley,<sup>10</sup> some efferent fibers in the optic chiasm govern chemical changes in the retina and also movements in the retinal pigment cells. Weiss<sup>11</sup> is inclined to agree with Ornstein's hypothesis and reports that treatment of such patients with glandular extracts, chiefly thyroid and pituitary, results in improvement of some cases. Zondek<sup>12</sup> called attention to the fact that a hormone from the pars intermedia of the hypophysis has been shown to affect the melanophores of frogs and also the pigment cells of fishes. He reported 4 patients with retinitis pigmentosa who gave evidence of pituitary obesity or cachexia and psychic depression. Treatment with prolan was tried, but without much success. Belskij and Jalin<sup>13</sup> reported 7 cases of retinitis pigmentosa with changes in the sella turcica, deposits of calcium in the bones of the hands and feet, and increased blood calcium apparently resulting from parathyroid disturbance. They stated that calcium iontophoresis was of benefit in these cases.

It has been demonstrated by a number of observers that night blindness is a rather constant symptom among patients and experimental animals who are deprived of vitamin A. The normal retina has been shown to store a large amount of vitamin A, and apparently the regeneration of the visual purple is dependent on the presence of this vitamin in the retina. The apparent increased sensitivity to light of the pigment cells of the skin and retina, demonstrated by Venzella<sup>14</sup> in cases of retinitis pigmentosa, may indicate a lowered capacity for the regeneration of the visual purple. Night blindness has been shown to occur among pregnant women whose diet is low in vitamin A. Henderson<sup>15</sup> reported a case of retinitis pigmentosa and retinitis punctata albescens in which the condition progressed markedly during pregnancy.<sup>16</sup> I reported a case of retinitis pigmentosa in which the field defects progressed definitely during the last month of pregnancy and returned to their previous status after the termination of pregnancy. These findings have suggested that the addition of large amounts of vitamin A to the diet might have a favorable influence on the course of retinitis pigmentosa. Levine<sup>17</sup> reported, however, that he had no success in a series of patients treated with large doses of cod liver oil over a con-



siderable period of time. Wilder<sup>18</sup> has suggested that in these cases there may be a defect in the capacity of the retina for storage of vitamin A, and that the use of a ketogenic diet might increase this storage capacity. One patient has been treated along these lines at The Mayo Clinic with apparent good results, and this method of treatment seems worthy of further trial. Satanowsky notes that the rods, and probably the cones, function through means of the visual purple, that the visual purple is soluble in bile acids and their salts, and that lack of vitamin A interferes with its regeneration. She reported 3 cases of retinitis pigmentosa in which there was disturbed hepatic function and stated that liver therapy is of benefit in these cases. Kestenbaum<sup>19</sup> treated a patient with ovosan to produce hyperemia of the retina, and with liver to increase retinal metabolism; he obtained favorable results.

In spite of the opinion of most histologists that interference with the retinal or choroidal circulation is not a primary factor in the pathogenesis of retinitis pigmentosa, it seems to be true that the most favorable results in the treatment of this disease have been obtained through the use of methods for the production of vasodilatation in the retina and choroid. Histologically, Asher<sup>20</sup> found thickening of the connective tissue of the choroid in the macular region, narrowing of the vessels with changes in their walls, marked changes in the pigmented epithelium, complete destruction of the neuroepithelium, collections of pigment in the walls and lumens of the retinal vessels, atrophy of the optic nerve, and thickening of the walls, with narrowing or occlusion of the lumens, of the vessels in the nerve head. He was of the opinion that these changes fit in better with the theory of primary injury to the capillaries of the choroid and retina than with the theory of abiotrophy of the neuroepithelium, or with that of a primary degeneration of the pigmented epithelium. Mariotti and Lugli<sup>21</sup> reported improvement in retinitis pigmentosa following retrobulbar injections of atropin, with resultant dilatation of vessels. Corrado<sup>22</sup> obtained improvement through the use of acetylcholin. Moreau was not successful in the treatment of 6 patients with hereditary retinitis pigmentosa by vasodilating methods, but in 2 cases in which the condition was associated with disease of the liver, marked dilatation of the vessels, with improvement in the field of vision, was produced by injection of acetylcholin into the vitreous. Wibaut<sup>23</sup> treated 31 patients with retinitis pigmentosa with menformon, which produces dilatation of the smaller arteries or capillaries. One patient showed marked improvement and 7 slight improvement. There was doubtful improvement in 13 cases and no improvement in 10. Von Heimburg,<sup>24</sup> however, found no improvement in 5 cases after the use of menformon.

Apparently the most efficient means of producing lasting dilatation of peripheral vessels is removal of sympathetic ganglions and section of the sympathetic trunks. It is generally accepted that the vessels of the retina are under the control of the cervical sympathetic nerves, and I<sup>25</sup> have demonstrated that dilatation of the arteries in normal retinas occurs in a high percentage of cases following cervicothoracic sympathetic ganglionectomy. Following the lead of Royle,<sup>25</sup> a number of operations on the cervical and thoracic sympathetic nerves have been performed in cases of retinitis pigmentosa. The results, in the main, have apparently been favorable. Royle reported 4 cases in which patients

were improved following division of the sympathetic trunk about the level of the second thoracic ganglion. In Meighan's<sup>27</sup> case the superior and middle cervical ganglions were removed along with the intervening trunk. In this case, as in Royle's cases, improvement in fields and vision was noted in both eyes though the operation was performed on only one side. This fact makes interpretation of the results rather difficult. Several patients have been operated on at the clinic, and the changes in the fields were far advanced. Subjective improvement was noted, but an objective widening of the peripheral fields could not be demonstrated. It would seem that the results obtained by various operators would justify a further trial of cervical or cervicothoracic sympathectomy, especially in the early stages of retinitis pigmentosa.

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## PHYSIOLOGY

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**Sulphur Metabolism. A Study of a Case of Cystinuria.**—JAMES C. ANDREWS and ALEXANDER RANDALL (Departments of Physiological Chemistry and Urology, University of Pennsylvania). A study has been made of the metabolism of sulphur compounds in a male cystinuric (age 14) using, as a control, a normal subject of the same age and sex.

The cystin output of the cystinuric is remarkably constant, and averages 0.09 to 0.10 gm. of cystin sulphur per day. This output is unaffected by the daily feeding of sodium bicarbonate or sodium citrate in amounts sufficient to keep the urinary pH between pH 7.0 and 7.5 although this alkalinity suffices to keep the cystin dissolved and to prevent calculus formation.

Daily administration of equimolar proportions of glycine and glutamic acid is without effect on the cystin output.

The use of a diet high in eggs (containing larger amounts of sulphur) does not raise the cystin output.

As has often been observed with other cystinurics, the present subject oxidizes cystin administered by mouth to sulphate and does not show any increase in urinary cystin output. In confirmation of the work of duVigneaud on the normal metabolic oxidation of the isomers of cystin, we find that the levo isomer is somewhat more rapidly and completely oxidized than the racemic mixture.

dl-Methionine is oxidized to sulphate to the extent of 60 to 80%; the remainder is excreted as unoxidized sulphur. In contradiction to the results reported by Brand and coworkers, we do not find that the administration of methionine to the cystinuric increases the cystin output. Direct determinations of methionine in the urine indicate that only a small proportion of the methionine which escapes oxidation to sulphate can be excreted as such. The remainder is excreted in some unknown form in which the sulphur is not oxidized to sulphate. The rate of oxidation and elimination of methionine sulphur by the cystinuric individual is much slower and more erratic than by the normal subject.

Cysteic acid, when fed to the cystinuric as well as to the normal subject, is excreted unoxidized.

The increase in the cysteine content of cystinuric urines on standing, when the cystine content is determined by the Sullivan procedure, has been noted by Brand and coworkers and has been ascribed by them to the excretion of part of the cystine in the form of an easily decomposed cystine complex. Without necessarily subscribing to this explanation, we confirm the results reported by Brand. We have observed that the cystine content of a freshly voided sample can increase, even on standing 24 hours at 0° C. and when preserved with chloroform, to from 25 to 50% over its original value. This higher value is maintained for at least several months.

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**Liebermann-Burchard Reaction Velocities of Sterols: I. Differences Between Free and Ester Cholesterol Applied to the Determination of Cholesterol Esters. II. A Test for the Presence of Coprostenol in Plasma.**—JOHN G. REINHOLD (Laboratory of Philadelphia General Hospital). Cholesterol esters and coprostenol (allocholesterol) develop color more rapidly than cholesterol when treated with acetic anhydride and sulphuric acid. The difference in reactivity of free and esterified cholesterol is increased by low temperatures and low concentrations of sulphuric acid. Higher temperatures and larger amounts of sulphuric acid cause such differences to become smaller and eventually to disappear. Based on these observations, a simple method has been devised for determination of cholesterol esters and total cholesterol in serum or plasma. The Liebermann-Burchard reaction, carried out at 0° C.

in the presence of 0.025 cc. sulphuric acid, is utilized for cholesterol ester determinations. These substances develop appreciable color intensities under such conditions, while free cholesterol produces very little color. Cholesterol oleate or palmitate solutions serve as standards for colorimetry. A correction is applied for color formed by free cholesterol.

Total cholesterol is found by warming the solutions to 38° C. for 30 to 40 minutes. Free and esterified cholesterol now yield equivalent concentrations of color, proportional to the total cholesterol contained in each solution.

Known mixtures of cholesteryl oleate and cholesterol have been analyzed correctly by this procedure. Cholesteryl oleate added to alcohol-ether extracts of serum can be recovered with fair success. Cholesterol ester determinations by the new method agree with results of gravimetric digitonin estimations. Total cholesterol figures are slightly high, particularly in jaundice.

Coprostenol (allocholesterol) if present, would be determined as cholesterol ester. The close agreement between colorimetric ester analysis and gravimetric determinations indicate that this substance does not exist in plasma. However, loss of coprostenol has not been entirely excluded.

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**The Secretion of Dyestuffs by the Kidney.**—R. HÖBER (Marine Biological Laboratory, Wood's Hole and Laboratory of Physiology, University of Pennsylvania). The tubules of the aglomerular kidney of the toadfish are permeable to a number of diffusible acid dyestuffs. After intramuscular injection some of them (Orange R, Azofuchsin S, Brillantorange R, Tropaeolin 0002, Echtrot A, Ponceauròt and Indigo-carmin) are concentrated in the lumina to such a degree that they appear as deeply colored threads in strong contrast to the colorless or faintly colored epithelial walls. The normal appearance of functional dyestuff concentration in the frog's kidney does not differ from that in the kidney of the toadfish. The usually observed picture after the injection of a dyestuff into the frog, significant by the accumulation of a great number of brightly colored granules in the epithelium of the proximal convoluted tubules, is the result of abnormal conditions, the granules representing dead spaces in the epithelial body. As in the toadfish, the acid dyestuffs enter the cells of the proximal tubules in the frog from the side of the venous capillaries and not from the side of the lumina; this can be demonstrated by injection of Diaminreinblau or Benzoblau 3B, two dyestuffs which cannot pass through the glomeruli, but are found to be stored in the cells of the proximal tubules.

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**Note on Reflex Thresholds in the Cat During Spinal Shock.**—G. P. MCCOUCH, W. J. SNAPE, and W. B. STEWART (Laboratory of Physiology, University of Pennsylvania). Divinyl ether, due to its rapid elimination, is a suitable anesthetic for transection designed for the study of the initial phase of spinal shock.

The transient depression following spinal transection under divinyl ether in the full grown cat involves the reflex thresholds studied in the following order of severity: ipsilateral extension elicited from the exter-

nal aspect of the thigh, little or not at all; ipsilateral flexion, relatively little; crossed flexion, moderately; crossed extension, severely.

Of these reflexes, the first three are present immediately after transection. Crossed extension may appear at any interval from 20 minutes to more than 24 hours. The lateness of its appearance is probably due partly to spinal shock, partly to inhibition from the crossed flexion reflex. Similarly, the ipsilateral flexion reflex, though relatively little affected by shock, does not extend its receptive field effectively over that of the still less involved antagonistic reflex from the external aspect of the thigh for several days after transection.

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ORIGINAL ARTICLES.

THE CLINICAL VALUE OF ALTERNATE SUCTION AND PRESSURE  
IN THE TREATMENT OF ADVANCED PERIPHERAL  
VASCULAR DISEASE.

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FROM the therapeutic standpoint patients with peripheral vascular disease can be divided into two groups: (a) Those whose symptoms are due to simple spasm with no, or very slight, organic vascular obstruction; and (b) those whose symptoms are due primarily to advanced organic disease of the arteries. The symptoms of the first group can usually be alleviated by producing vasodilatation with drugs, diathermy, contrast baths, local heat in the form of the warm cradle, or finally with sympathetic ganglionectomy. The efficacy of these therapeutic procedures depends upon local dilatation of the peripheral bloodvessels.

In the later stages of peripheral vascular disease the walls of the arteries become thickened and more or less rigid. They have not only abnormally small lumina, but are also unable to dilate even when vasoconstrictor tone is abolished by nerve block or by sympathetic ganglionectomy. Under these conditions the therapeutic procedures mentioned above are much less likely to increase blood flow, and they usually fail to improve the nutrition of the tissues (Adson and Brown;<sup>1</sup> Morton and Scott<sup>2</sup>). Eventually most patients with

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advanced organic disease of the arteries suffer from trophic changes, ulceration and gangrene, leading finally to amputation. They often present a difficult therapeutic problem to both the clinician and the surgeon.

Landis and Gibbon<sup>3,4</sup> found that the digital skin temperatures of the lower extremities of patients with advanced organic vascular occlusion could be elevated by applying alternate suction and pressure to the affected extremity. Preliminary studies indicated that to increase blood flow most efficiently it was advisable to have: (1) Relatively brief periods of suction; (2) brief periods of pressure; and (3) diminished vasoconstrictor tone. Landis<sup>5</sup> observed that this procedure relieved to some extent the clinical manifestations of the ischemia which accompanies organic vascular occlusion.

This paper describes the results of treating a series of patients by means of alternate suction and pressure, with particular reference to the limitations and the possible usefulness of this procedure in the therapy of peripheral vascular disease.

A conservative general estimate of the clinical results so far bears out the encouraging experimental findings in that: (1) The rest pain of ischemia was relieved, at least temporarily; (2) intermittent claudication, when present, became less intense and did not appear so soon in the course of exercise; and (3) indolent ulcers or superficial gangrene often healed in a manner not observed with the usual modes of treatment. Changes in skin color could not be measured quantitatively, but various observers agreed that cyanosis often diminished and that skin color approached normal during the progress of treatment.

**I. Selection of Patients and Methods Used.** Suction and pressure was applied to the extremities of 29 patients suffering from advanced peripheral vascular disease with pain and ulceration. These patients had shown little progress under the usual conservative treatments, including local warm applications, the warm cradle, antiseptics, vasodilator drugs, or even nerve section. An excessively long period of hospitalization or mutilating surgery seemed to be the only alternative. Those treated in the Philadelphia General Hospital were chiefly diabetics from the metabolic wards, while most of the patients treated in the University of Pennsylvania Hospital suffered from arteriosclerosis, or thromboangiitis obliterans.

The grade of organic occlusion was tested whenever possible by the method of Landis and Gibbon;<sup>6</sup> abnormal findings were checked when necessary by peripheral nerve block (Scott and Morton<sup>7</sup>). In some instances the vasodilator response was tested at intervals during the use of suction and pressure therapy to study objective changes in the circulation of the extremity under observation.

The apparatus used for treating patients in both hospitals was the same as that described by Landis and Gibbon<sup>4</sup> and Landis.<sup>5</sup> During treatment the patients sat or reclined in bed. The affected

extremity was inserted into the aluminum chamber and lay in the horizontal plane upon a pillow in the bottom of the chamber. The extremity could be inspected through the glass top of the box to detect changes in skin color occurring during treatment. The thigh, protected when necessary by a layer of gauze bandage, was encircled at a point 6 inches above the knee by a rubber cuff with two leaves, one sealing during pressure, the other sealing during suction. A layer of adhesive tape was applied to each cuff to keep the rubber in close contact with the skin.

Since the effect of suction and pressure on skin temperature had already been studied in patients with peripheral vascular disease (Landis<sup>5</sup>), no effort was made to control the temperature of the air surrounding the limb in the chamber. The air compressor became warm after running some minutes; consequently the air temperature in the aluminum chamber rose gradually to between 25° and 29° C. One forearm was encircled by an electric heating pad to reduce reflexly the vasoconstrictor tone in the lower extremities so that an adequate reservoir might be available for accommodating arterial blood drawn into the peripheral vessels during suction. The patients usually perspired slightly during the period of treatment.

Suction amounting to between 80 and 120 mm.Hg (*i. e.*, below atmospheric pressure) was applied for 25 seconds alternately with pressure of 60 to 80 mm.Hg (*i. e.*, above atmospheric pressure) for 5 seconds. The time required to change the air pressure within the aluminum chamber from -120 to +80 mm.Hg was reduced to about 3 seconds in order that as little time as possible should be lost in changing from suction to pressure. The time relations of the pressure variations have already been shown diagrammatically (Landis,<sup>5</sup> Fig. 6). Unless otherwise mentioned, -120 and +80 mm.Hg were used for 25 and 5 seconds, respectively. Until patients became familiar with the apparatus it was usually expedient to use -80 and +60 mm.Hg for 25 and 5 seconds, respectively. In a few instances, -150 and +100 mm.Hg were used for 50 and 10 seconds, respectively, without discomfort or injury.

In general when rest pain was severe, or when ulcers had not yet begun to heal, the affected extremities were exposed to suction and pressure for 2 hours, twice daily. If rest pain was very severe, treatment was given even more frequently, and over longer periods. Occasionally for severe nocturnal rest pain, suction and pressure therapy was used at night for as long as 6 hours continuously. After rest pain had diminished somewhat and after ulcers had begun to heal, the duration of treatment was reduced to 1 or 2 hours, at first once daily, then 3 times weekly and finally to 2 hours once weekly.

Ulcers were dressed daily with vaselin gauze; antiseptics were used only rarely, since even the mildest appeared to delay the growth



of granulation tissue and epithelium in ischemic extremities. Parts involved in dry gangrene were merely covered with sterile gauze. Nearly all patients had been treated by means of the warm cradle for days or weeks before suction and pressure therapy was used; the use of the warm cradle was continued during the intervals between suction and pressure treatments.

**II. Clinical Observations.** Observations on the treatment of 29 patients have been arranged in a series of tables, grouped according to clinical diagnosis. The patency of the peripheral vessels is described under the heading, Vasodilator Response, by recording the maximum skin temperature reached during vasodilatation if a measurable rise occurred. The notation 0 indicates that skin temperature continued to fall, or did not rise at all during the period when vasoconstrictor tone was abolished. The total duration of treatment is given in terms of the number of hours during which the extremity was actually exposed to suction and pressure. The left and right portions of each table describe the status of the patient before and after the application of pressure variations, respectively. The last column gives a clinical estimate of the usefulness of suction and pressure in each instance. The general results will be considered according to diagnosis.

**Results. A. Diabetes.** A total of 14 diabetic patients were treated, 9 having painful, indolent ulcers or gangrene (Table 1), 5 having rest pain but no ulceration (Table 2). The diabetes was kept adequately under control during treatment. Table 1 indicates the clinical findings and results in the presence of ulceration or gangrene. Six of these patients were referred for treatment of ulcers which had failed to show evidence of healing during periods of 6 weeks to 4 months. Two complete failures were encountered. In 1 instance (Case 1) a large, deep ulceration healed, pain became less but slowly progressing osteomyelitis eventually required amputation of the leg. In the other failure (Case 7), 2 of 3 ulcers healed, pain was relieved temporarily; but a large slough in the floor of the third and most extensive ulcer failed to soften, pain again increased and the leg was amputated.

The remaining 7 patients with ulcers improved conspicuously. Rest pain, originally present in 6 cases, was relieved permanently in 5 and temporarily only in 1. Cyanosis decreased and lesions, previously stationary, healed often with considerable rapidity after suction and pressure therapy was begun. Protocol 1 (Case 3) exemplifies this group. Photographs taken before and after treatment of Cases 2, 3 and 4 are shown in Figs. 1, 2 and 3, respectively.

Table 2 summarizes the results in 5 diabetics without lesions. Rest pain and claudication diminished in 4. Case 14, treated for only 6 hours, showed no improvement but at a later period more adequate treatment was followed by relief from discomfort at rest, though claudication was but slightly affected.

TABLE 1.—DIABETES, ARTERIOSCLEROSIS, WITH ULCER OR GANGRENOUS SLOUGH (9 CASES).

Case, sex and age (yrs.).	Additional diagnoses; duration of lesion.	Before treatment.						After treatment.						Result.	Remarks.	
		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.	Suction-pressure treatment, hrs.	Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.			Gangrenous slough.
1. M., 54	Early osteomyelitis; ulcer on side of foot. 4 mos.	0	..	++	++	0 (deep)	0	100	0	..	0	++	Small sinus	0	Poor	Ulcer healed; pain controlled; osteomyelitis progressed slowly; amputation of leg.
2. M., 63	Myocardiosis, edema; gangrene surface of toe. 6 wks.	0	..	++	++	1.5	Dry plaque	21	0	..	0	++	0	0	Good	Lesion stationary for 6 wks. prior to suction-pressure; no recurrence in 6 mos.
3. M., 80	One leg amputated previously; necrotic ulcer. 3 mos.	0	0	0	++	1.5 (deep)	0	40	0	0	+	+	0	0	Good	Extreme occlusion; healing began late; necrotic toe lesion began 6 mos. later. Healing accelerated.
4. F., 59	Slough on great toe from hot water bag. 3 wks.	++	..	0	++	1.3	Plaque	37	++	+	0	+	0	0	Good	Indolent lesion; responded only to suction-pressure; varices not affected.
5. F., 42	Hypertension, varicose veins; pressure necrosis of heel. 2 wks.	0	..	++	0	0	Large plaque	23	0	..	0	0	0	0	Good	Pain relieved; injury to leg on ward interrupted treatment; ulcer continued to heal.
6. F., 47	One toe amputated previously; spontaneous ulcer of toe. 2 wks.	++	..	++	*	1.0	0	14	++	..	0	*	0	0	Fair	Temporary relief of pain; healing of 2 ulcers; persistent slough required amputation.
7. M., 58	Ulcers, (a) under malleolus, (b) great toe, (c) heel. 24 mos.	0	0	++	++	2.3 (a) deep (b) 0 (c) 0	(a) deep (b) 0 (c) 0	62	0	0	0 to ++	+	(a) open (b) 0 (c) 0	(a) + (b) 0 (c) 0	Poor	Ulceration, previously enlarging, healed completely.
8. M., 78	Previous amputation of rt. leg; ulcers, (a) toe; (b) interdigital space. 4 mos.	0	0	++	++	0.3 (a) + (b) 0	(a) + (b) 0	37	0	0	0	0	0	0	Good	Incomplete; patient died at home of intercurrent pneumonia.
9. M., 62	Indolent ulceration of great toe	++	6.1 °C.	0	++	1.5	0	50	++	..	0	+	0.5	0	Good	

++ + + + to 0 = degree of intensity of symptom or sign.

\* Negroes.

TABLE 2.—DIABETES, ARTERIOSCLEROSIS, WITH REST PAIN AND CLAUDICATION BUT NO LESION (5 CASES).

Case, sex and age (yrs.).	Additional diagnoses; duration of symptoms.	Before treatment.					Suction-pressure treatment, hrs.	After treatment.					Remarks.	
		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.		Result.
10. M., 64	Mild osteoarthritis; rest pain and intermittent claudication, 2 yrs.	0	.	++	50	++	18	0	31° C	0	300	++	Good	Relief of pain; no objective changes.
11. M., 57	Arterial occlusion; sec- ondary anemia, 1 yr.	0	0	+	100	+	14	0	0	0	600	+	Good	Relief of pain; claudication delayed; no objective changes.
12. F., 68	Sudden thrombosis; con- stant pain, 2 wks.	0	.	Rubor +++	.	Rubor +++	12	0	.	0	.	Rubor +++	Good	Relief of pain; foot warmer; color less intense; reinter- ced with gangrene of toe 4 mos. later.
13. M., 55	Alcoholism; thrombosis of partly occluded artery; pain, 4 wks.	0	.	+	.	+	10	0	.	0	.	0	Good	Relief of pain; tided over stage of acute ischemia.
14. F., 67	Cramps at night; claudi- cation	0	0	++	50	++	6	0	.	+	50	+	Poor	Treatment period brief; cramps relieved; claudi- cation unaffected.

Relief of pain; no objective changes.

Relief of pain; claudication delayed; no objective changes.

Relief of pain; foot warmer; color less intense; resected with kangrene of toe 4 mos. later.

Relief of pain; tiled over stage of acute ischemia.

Treatment period brief; cramps relieved; claudication unaltered.

*B. Thromboangiitis Obliterans.* Eight patients with thromboangiitis obliterans (Table 3) were treated for between 5 and 81 hours on account of ulceration accompanied by rest pain (7 cases) and claudication (4 cases). Two patients (Cases 20 and 21) suffered from ulcers which had persisted some months after nerve section. The general results were excellent in 4 instances, good in 1 and fair in 2. Ulcers healed, cyanosis became less, rest pain gradually disappeared and the severity of intermittent claudication was diminished.

Case 17 (see Protocol), though recorded as a failure, should probably not be thus classified. This patient entered the hospital with a massive gangrenous slough extending to the middle of the right palm, following amputation of the index finger at another hospital. Conservative treatment was out of the question but the patient refused operation until several days after admission. During this period the effects of suction and pressure therapy on severe rest pain were observed with the temporary relief indicated in Protocol 2. The patient finally permitted amputation above the elbow.

Case 18 suffered from dry gangrene of the tip of one toe with severe rest pain. Relief of pain, though striking, was only temporary and the toe was amputated at its base. The patient returned several weeks after operation with renewed pain; suction and pressure therapy was used to aid healing of an indolent ulcer which had persisted at the site of amputation.

Three patients with thromboangiitis obliterans but with no ulceration (Table 4) were treated, 1 for rest pain and 2 for intermittent claudication. Rest pain disappeared, intermittent claudication became less intense and did not appear so soon in the course of exercise.

*C. Arteriosclerosis.* Three patients hospitalized for lesions associated with arteriosclerosis of advanced grade were treated, with failure in 1 instance and with excellent results in 2. The patient in whom amputation was eventually necessary presented dry gangrene of the toe with excruciating rest pain. Suction and pressure therapy was used for a total of 2 hours over short periods. Rest pain was absent during the use of suction and pressure but returned during the intervals between treatments. The associated polycythemia and varicose veins made permanent benefit very unlikely so that amputation was resorted to without further trial of suction and pressure therapy. Case 28 complained of severe pain which was relieved on several occasions within a few minutes after suction and pressure therapy was started. The ulcers in this patient had previously been enlarging but began to heal quite promptly and closed completely after 91 hours of therapy.

One patient (Case 29; see Protocol) presented on admission marked slaty cyanosis of the great toe with excruciating pain controlled only partially by opiates in moderate dosage. Amputation

TABLE 3.—THROMBOANGITIS OBLITERANS WITH REST PAIN AND ULCERATION (8 CASES).

Case, sex and age (yrs.)	Additional diagnoses; duration of lesion.	Before treatment.					After treatment.						Remarks.						
		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.	Suction-pressure treatment, hrs.	Palpable arterial pulse.	Vasodilator response.	Pain.		Claudication, yds.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.	Result.	
15. M., 26	Ulcer of toe, 9 wks.	0	30 5° C (slow)	+++	300	0	2.2	0	35	0	...	0	0	0	0	0	0	Good	Complete relief of constant pain; probably aided by hypertonic saline solution intravenously.
16. M., 30	Amputations; large ulcer dorsum of foot, 5 mos.	0	...	++	..	+++	5.6	0	14	0	...	+	..	++	3.2	0	0	Fair	Incomplete; patient left hospital against advice.
17. M., 53	Multiple amputations previously; gangrenous sloughing ulcer of hand; osteomyelitis	0*	0	+++	..	+++	6.0	+++	5	0	...	0 (in pump) +++	..	+++	+++	6.0	+++	Poor	Conservative treatment forced by patient against advice; pain relieved only while in apparatus; amputation of arm.
18. M., 28	Gangrene, tip of 2d toe	0	0	+++	..	+++	0.9	++ (dry)	11	0	0	0 (in pump) ++	..	+++	+++	0.9	+	Poor	Pain and slow increase in area of gangrene; amputation of toe; see next line.
	(a) Indolent ulcer after amputation of 2d toe; (b) ulcer below malleolus	0	0	+++	..	+++	(a) 1.5 (b) 1.0	++	81	0	0	++	..	0 to ++	0	(a) 0 (b) 0	0	Good	Ulceration, previously painful and indolent, healed; pain relieved.
19. M., 41	Previous amputation rt. 1st toe; indolent ulcer, osteomyelitis of 2d toe	0	28° C (slow)	++	100	+++	0.4	0	14	0	...	0	..	+	0	0	0	Fair	Osteomyelitis prevented complete closure of ulcer; minute sinus remained; pain and claudication relieved.
20. M., 37	Chronic ulcer, toe, enlarging after nerve section for pain, 5 mos.	0	0	0	30	+++	1.8	+	71	0	0	0	0	+	0	0	0	Good	Complete healing after all other treatment had failed; amputation advised but refused.
21. M., 48	Chronic ulcer, toe, 5 mos. after nerve section for pain	0	0	0	30	+++	1.0	+	60	0	0	+	0	0	0	0	0	Good	Claudication relieved; ulcer healed after minor recurrence.
22. M., 53	Chronic ulcer, 4th left finger	0*	0	+++	..	+++	1.0	+	22	0	31.2° C (slow)	0	..	0	0	0	0	Good	Indolent sloughing ulcer, previously treated without result, healed rapidly.

\* Radial and ulnar arteries.

TABLE 4.—THROMBOANGITIS OBLITERANS, WITH REST PAIN, CLAUDICATION, BUT NO LESION (3 CASES).

Case, sex and age (yrs.).	Before treatment.					Suction-pressure treatment, hrs.	After treatment.				Result.	Remarks.
	Palpable arterial pulse.	Vaso-dilator response.	Pain.	Claudication, yds.	Cyanosis.		Palpable arterial pulse.	Vaso-dilator response.	Pain.	Claudication, yds.		
23. M., 46	0	29° C.	++	...	+	2½	0	29.5° C.	0	...	+	Subjective relief; previous amputation prevents walking. Typhoid vaccine; diathermy; baths tried previously without effect. Diathermy; baking used without effect.
24. M., 58	0	24° C.	0	30	0 to +++	2½	0	26.0° C.	0	1000	0 to ++	
25. M., 43	0	26° C.	0	30	0 to +++	112	0	27.0° C.	0	100	0 to ++	

Subjective relief; previous amputation prevents walking.  
Typhoid vaccine; diathermy; baths tried previously without effect.  
Diathermy; baking used without effect.

TABLE 5.—ARTERIOSCLEROSIS, WITH REST PAIN, ULCER, OR GANGRENOUS SLOUGH (3 CASES): REST PAIN, NO LESION (1 CASE).

Case, sex and age (yrs.).	Additional diagnoses; duration of lesion.	Before treatment.						Suction-pressure treatment, hrs.	After treatment.						Result.	Remarks.
		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		
26. M., 78	Large active ulcer exposing tendons, side of foot. 2 mos.	0	:	0	++	3.0	0	15	0	:	0	+	0	0	Good	Gelatin boot for support probably aided healing; boot alone ineffective.
27. M., 60	Polycythemia; hypertension; varicose veins	0	:	+++	+++	0	Plaque	2	0	:	0 (in pump) + + + + (out) 0	+	0	Same	Poor	Varicose veins made relief unlikely; amputation of leg.
28. M., 63	Sloughing ulcers (a) 2d toe, (b) 3d toe	0	0	+++	*	(a) 0.9 (b) 0.8	(a) + (b) 0	91	0	:	0	*	(a) 0 (b) 0	0	Good	Severe pain at night relieved by treatment, with eventual healing of ulcers.
29. M., 65	Myocardosis, angina; agnizing pain. 2 wks.	0	0	+++	+++	0	Blebs	46	0	:	0	0 to ++	0	0	Good	Severe rest pain and threatened gangrene relieved during suction-pressure therapy.

\* Negro.

seemed hazardous on account of associated myocardial weakness, angina pectoris and generalized arteriosclerosis. Suction and pressure therapy was instituted with the result that pain diminished rapidly and cyanosis disappeared. The patient was discharged free of rest pain. The foot still showed slight cyanosis in the dependent position, but the previous gray dusky cyanosis had disappeared. A summary of this patient's record is given in Protocol 3.

TABLE 6.—GENERAL SUMMARY.

Diagnosis.	Relief of symptoms and signs.			Total.
	None.	Fair.	Good.	
Diabetes:				
With ulceration . . . . .	2	1	6	9
Without ulceration . . . . .	1	0	4	5
Thromboangiitis obliterans:				
With ulceration . . . . .	2	2	5	9*
Without ulceration . . . . .	0	1	2	3
Arteriosclerosis:				
With ulceration . . . . .	1	0	2	3
Without ulceration . . . . .	0	0	1	1
Totals . . . . .	6†	4	20	30*

\* Case 18 was treated before and after amputation of toe. Results have, therefore, been entered in 2 columns.

† Poor results associated with: (a) Osteomyelitis in 1 case; (b) gangrenous slough in 4 cases; (c) very brief period of treatment in 1 case.

*D. Effect of Suction and Pressure on the Various Clinical Manifestations of Ischemia.* Table 6 summarizes the general results more briefly. In 29 patients treated with suction and pressure, amputation was performed in 5, and 1 patient was not aided by a period of treatment which was too brief to be considered a fair trial. Thus, 6 patients were aided not at all or only temporarily; in none was there evidence of harm arising from the use of suction and pressure. In the 5 patients coming to amputation a massive gangrenous slough was present in 4, and extending osteomyelitis in 1. Attempts to arrest an early osteomyelitis failed completely even though the cutaneous lesion healed except for a sinus kept open by exudate from the infected bone (Table 1, Case 1; Table 3, Case 19). The results indicate also that deep gangrene makes it unlikely that suction and pressure therapy will be of permanent benefit. When gangrene involves more than the superficial tissues, suction and pressure therapy can do little more than reduce pain temporarily, and possibly put the adjacent tissues in better condition to withstand amputation. The history of Case 18 (Table 3) suggests that after amputation of a digit suction and pressure therapy may make it possible in some instances to avoid more extensive mutilation. The less severe manifestations of ischemia—cyanosis, rest pain, intermittent claudication and indolent ulceration—diminished in many patients during the period when suction and pressure therapy was used.

When patients are first treated, changes in skin color may become obvious almost at once, but more often cyanosis is affected only after several hours of treatment. In a few cases, subjective relief was obtained without any clearly demonstrable modification of skin color.

The effect of suction and pressure on cyanosis seems to depend upon the grade of organic vascular obstruction. In a limb which is ischemic by reason of vascular spasm accompanied by moderate organic obstruction, cyanotic digits often become pink during the first few alternations of pressure. On several occasions when Case 25 (Table 4) came in from out-of-doors (temperature, 18° to 15° C.), both lower extremities were extremely cold and the skin of both feet was intensely pale and cyanotic. The left extremity (the more diseased) was placed in the apparatus, while the other remained in room air at the same temperature. Suction and pressure were applied in the usual way. At the end of the first period of suction the foot became deeply red except for the second, third and fourth toes which still remained pale and cyanotic. The second suction period produced redness of the fourth toe and of the bases of the second and third toes. The fourth suction period reddened all the skin of the foot excepting that at the tip of the third toe. One minute later this digit was also normal in color. The other extremity meanwhile remained pale and cyanotic.

When advanced organic obstruction is present (*e. g.*, Case 8, Table 1), digits, originally cyanotic, will gradually become normal in color as blood invades the skin from the base of the digit. The progress of this change in color is very much slower, but it can be followed from day to day and is naturally subject to changes in environmental temperature. The hyperemia which accompanies suction may finally become almost as pronounced as in normal skin. The color changes are often striking enough to be noticed spontaneously by the patients themselves. Normal skin color, once induced, usually persists even during the winter months.

Those areas of skin which are actually necrotic exhibit no change in color. Presumably local asphyxia has produced thrombosis and stasis, closing the vessels permanently so that blood flow cannot be resumed even with external physical aid.

Lewis *et al.*<sup>8</sup> produced pain in normal subjects by exercise while blood flow was restricted. Restoration of blood flow quickly relieved this pain. Since suction and pressure therapy increases blood flow, as indicated by elevation of skin temperature, it should also alleviate rest pain in a relatively short time. The immediate effects on rest pain have been described (Landis<sup>5</sup>) and are illustrated in Protocol 2. In the many hours during which suction and pressure have been used, rest pain has been in general strikingly relieved during the period of treatment. This relief proved to be only



temporary when massive gangrene or large gangrenous sloughs were present. The pain of neuritis was not affected.

Patients with indolent or slowly enlarging ulcers, but without frank gangrene, large sloughs or extending necrosis, obtained more lasting relief from rest pain. As a rule, patients exhausted by continued pain fall asleep while the extremity is in the apparatus. Sleep ordinarily became possible without sedatives after a few days.

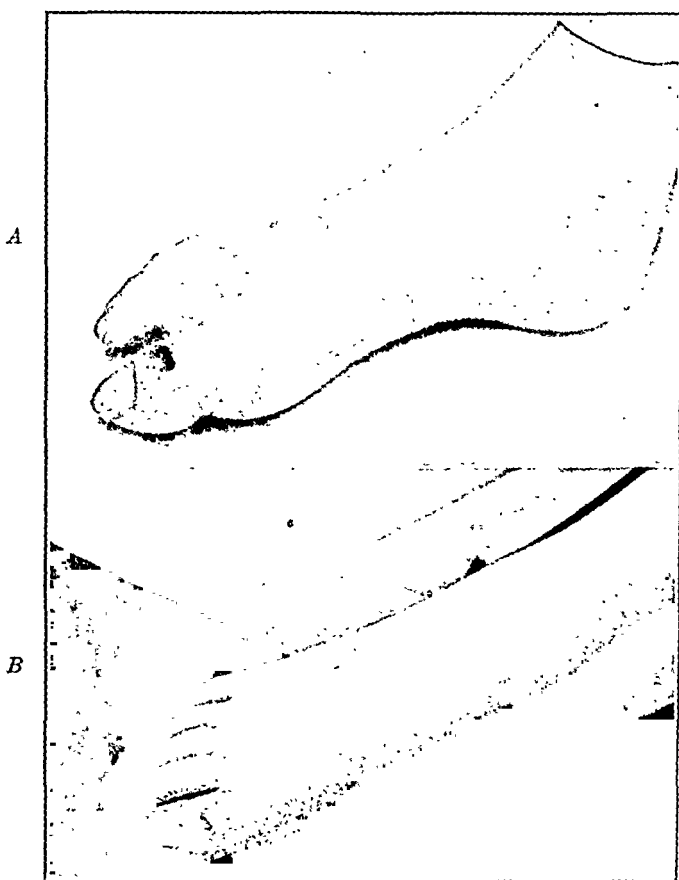


FIG. 1.—Patient R. S., Table 1, No. 2, showing lesion: (A) After ordinary conservative therapy for 6 weeks; and (B) after suction and pressure therapy, totaling 24 hours in 3 weeks.

Discomfort may arise during treatment if ulcers are allowed to dry; this can be avoided by covering raw areas with vaselin with or without bandage.

The continuous use of suction and pressure was attempted on several occasions. Unfortunately, however, the type of cuff used in these studies cannot be tolerated for more than a few hours and immobilization of the extremity becomes extremely irksome after 2 or 3 hours. Until a more comfortable cuff is available, suction

and pressure therapy should not be used routinely for more than a few hours without interruption.

The effects of suction and pressure on intermittent claudication were difficult to evaluate and have been in general less striking, though slow improvement was observed as a rule. The subjective nature of the symptoms in intermittent claudication and the possibility of spontaneous recovery make it advisable to reserve judgment concerning the usefulness of suction and pressure therapy in treating this particular form of pain.

The effect of suction and pressure on actual lesions arising from prolonged ischemia depend upon the type of lesion. Patients with frank gangrene did not improve significantly during or after exposure to pressure variations. One patient with a large sloughing ulcer under the malleolus showed temporary improvement, but slow extension of the slough and renewed pain after several weeks made amputation eventually necessary. Those patients who had indolent ulcers without frank gangrene and without large sloughs were markedly improved. The ulcers under observation had, in some instances, been indolent or enlarging under treatment with antiseptics and heat for periods of several months before pressure variations were used.

**Protocols.** CASE 3.—(Table 1.) M. T., male, aged 60, with mild diabetes of unknown duration, developed a necrotic ulcer on the lateral aspect of the right heel while convalescing from the amputation of his left leg for gangrene at another hospital. The necrosis extended deeply; the lesion had not changed during 3 months' conservative treatment.

On admission to the Philadelphia General Hospital, physical examination showed retinal and peripheral arteriosclerosis with popliteal pulsation but no palpable pulse in the foot. Roentgenography revealed conspicuous calcification of the pedal arteries. The foot was not painful and was cyanotic only when dependent. No vasodilator response was obtained when vasoconstrictor tone was abolished, indicating that marked organic arterial occlusion was present. The punched-out ulcer was not tender and measured 1.5 cm. in diameter (Fig. 2A).

After 40 hours of treatment with alternate suction and pressure ( $-120$  and  $+80$  mm.Hg) during 6 weeks, the ulcer had healed completely (Fig. 2B) without modification of skin color. Anesthetization of the posterior tibial nerve still produced no elevation of skin temperature.

In this instance an ulcer unimproved by 3 months of usual treatment healed during suction and pressure therapy.

CASE 17.—(Table 3.) C. D., white male, aged 53, was admitted to the University Hospital on January 25, 1934. Since 1926, when the diagnosis of thromboangiitis obliterans was first made, the patient had undergone a series of amputations of fingers and toes. Certain of these amputations followed lumbar sympathectomy.

In December, 1933, the index finger of the right hand became painful and an ulcer formed at its tip. The finger was amputated, December 16, 1933, at another hospital. Operation was followed by infection of the palm, swelling of the whole hand and increased pain, particularly after the palm was incised for drainage.

On admission the patient complained of agonizing pain in the right hand. A large gangrenous slough extended from the base of the thumb to the base of the third finger. The distal cut end of the proximal phalanx of the second finger protruded from the middle of a slough which penetrated deeply into the middle of the palm. The other fingers of the right hand were cyanotic and showed pits indicating previous localized necrosis. Arterial pulsation palpable in the elbow could not be followed to the wrist. A roentgenogram showed osteomyelitis of two metacarpals.

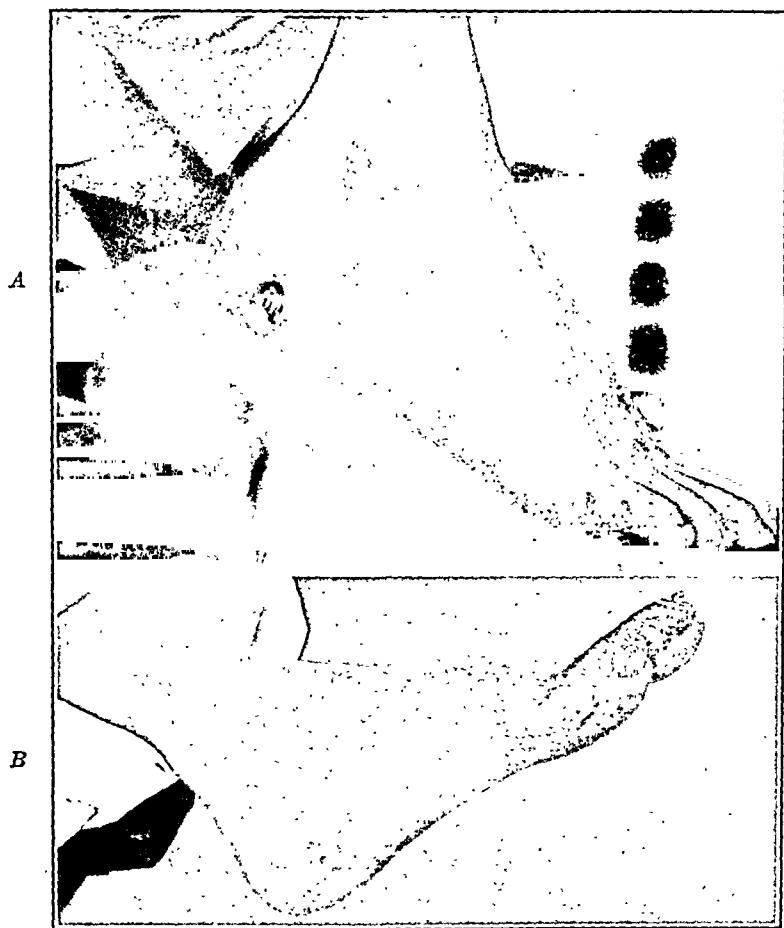


FIG. 2.—Patient M. T., Table 1, No. 3, showing lesion: (A) After ordinary conservative treatment for 3 months; and (B) after suction and pressure therapy, totaling 40 hours in 2 months.

Conservative treatment was regarded as completely hopeless, owing to the size of the slough and the well-developed osteomyelitis. There was no evidence of acute spreading infection though the whole hand was swollen and brawny as a result of previous infection. The patient absolutely refused to submit to amputation until 72 hours after admission. During this interval the right hand was exposed to suction and pressure to relieve rest pain if possible. When the patient lay in bed the hand could not be

held above the level of the sternum more than a few minutes without producing agonizing pain. On 2 occasions the right hand was placed in a modified aluminum box elevated above the sternum so that the hand assumed the position which, under ordinary conditions, became intolerable after a few minutes. Suction and pressure were applied while the hand lay in this position.

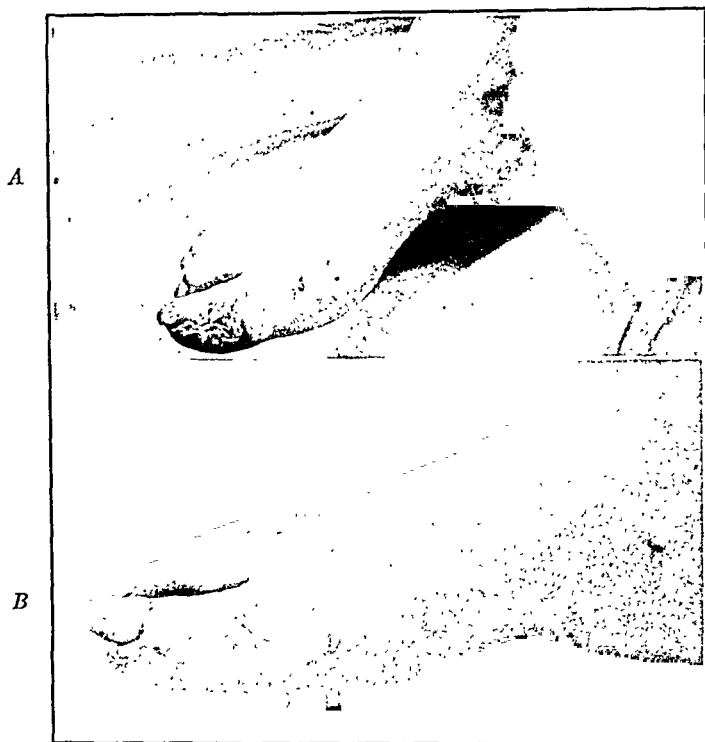


FIG. 3.—Patient C. L., Table 1, No. 4, showing lesions: (A) After ordinary conservative treatment for 3 weeks; and (B) after suction and pressure therapy, totaling 37 hours in 1½ months.

#### OBSERVATION 1, JANUARY 26, 1934.

- 12.15 P.M. Right hand placed in apparatus with sponge rubber cuff at a point halfway between the elbow and wrist. Suction (80 mm.Hg) and pressure (60 mm.Hg) applied alternately for 25 and 5 seconds, respectively.
- 12.30 P.M. No pain whatever.
- 1.45 P.M. No pain. Pump stopped for 2 minutes, followed by severe pain in palm.
- 1.47 P.M. Pump started again. Fingers still cyanotic with small red areas visible over palm.
- 1.48 P.M. Pain less.
- 1.49 P.M. Pain gone, itching remains.
- 2.30 P.M. Slight persistent pain in palm, not severe.
- 2.35 P.M. Hand removed. No severe pain at time of removal but pain returned later.

## OBSERVATION 2, JANUARY 26, 1934.

- 9.00 P.M. Pain present. Suction (90 mm.Hg) and pressure (70 mm.Hg) applied alternately for 25 and 5 seconds, respectively.
- 9.05 P.M. No pain.
- 9.35 P.M. Itching in palm, no pain.
- 10.00 P.M. Slight steady pain on back of hand and palm obviously not severe since patient slept most of the time.
- 10.03 P.M. Pump stopped, aluminum chamber opened to loosen bandage over wrist.
- 10.04 P.M. Severe pain.
- 10.05 P.M. Pump started, pain diminishing.
- 11.15 P.M. Entirely comfortable, sleeping at intervals.
- 11.40 P.M. Hand feels numb and tired, especially near wrist where cuff is situated.
- 12 MIDNIGHT. Discomfort and numbness due to pressure of cuff required removal of hand from the apparatus. Numbness and fatigue disappeared as soon as cuff was removed from the forearm.

Suction and pressure relieved rest pain temporarily on 3 occasions, but pain in the intervals, the magnitude of the slough and the osteomyelitis made amputation obligatory.

CASE 29.—(Table 5.) G. M., white male, aged 65, observed blueness of the left great toe in October, 1932, with numbness and pain in the ankle after exercise. During April, 1933, he experienced sharp, lancinating pain in the left great toe which continued with exacerbations so that continued sleep was impossible, even with opiates, for the 2 weeks immediately preceding admission.

On admission to the University Hospital on April 27, 1933, physical examination revealed emphysema, enlargement of the heart to the left and a blood pressure of 176 systolic and 74 diastolic. There was moderate generalized arteriosclerosis and no arterial pulsation could be felt in either foot. A vasodilatation test revealed marked organic vascular occlusion. A diagnosis of arteriosclerotic occlusion was made.

The affected toe was extremely painful, tender on even light pressure and deep slaty-blue in color. Its appearance was that of an early stage of gangrene. During the first 48 hours of hospitalization the pain was not appreciably affected by considerable sedative medication and a thermoregulated warm cradle.

From April 29 to May 9 suction and pressure therapy was used from 2 to 4 hours daily. No pain was experienced while the extremity was exposed to suction and pressure. The patient slept throughout the first few periods of treatment. Tenderness disappeared and cutaneous blebs originally present dried up without involving more than the superficial layers of the skin. Skin color changed only slightly at first, but later the area of cyanosis was rapidly invaded by rubor and eventually the whole toe was at times bright red in color, still becoming rather cyanotic, however, in the dependent position. By May 1, rest pain, formerly severe and continuous, was much milder and only occasional. There was almost no pain after May 7 sedatives being discontinued after May 6. The patient was discharged, May 27, 1933, after being free of pain for 2 weeks. The color of the left foot was practically normal at the time of discharge.

**Discussion.** The desirability of increasing local blood flow in certain medical and surgical conditions involving the extremities has long been recognized. Paré,<sup>9</sup> Nicoladoni,<sup>10</sup> Bier<sup>11</sup> and others induced venous congestion by applying a constricting bandage at the

base of the extremity. While this procedure increases the amount of blood trapped in the vessels distal to the bandage it does not increase, but really reduces, total blood flow if congestion is extreme (Stewart<sup>12</sup>). Junod<sup>13</sup> and Bier<sup>11</sup> placed the limb in a rigid box and produced venous engorgement by removing air slowly over a period of 2 to 3 minutes until the pressure about the limb was finally reduced considerably below atmospheric pressure. Hemorrhages appeared in the skin when the pressure was reduced too greatly during such prolonged suction, indicating that the peripheral vessels were conspicuously distended. Bier claimed no increase of blood flow for this procedure, properly regarding it merely as another method of producing passive congestion.

Direct measurements of capillary pressure (Landis<sup>14</sup>) indicated that the rate of blood flow in the capillaries of the frog's mesentery depends upon the steepness of the gradient of peripheral blood pressure. According to Poiseuille's law the amount of fluid flowing through a rigid tube depends upon the fall in pressure along the tube. On these grounds Landis and Gibbon<sup>3</sup> were the first to call attention to the theoretical possibility of increasing the peripheral fall in blood pressure by applying negative and positive pressure alternately to the surface of the lower extremity. It seemed likely that this procedure, if carried out under the proper conditions, might increase the amount of blood flowing past an arterial obstruction in unit time. In normal subjects these pressure variations increased blood flow and elevated skin temperature in the treated limb. The same procedure diminished the rate of cooling of an extremity originally warm, and usually caused an originally cold extremity to become warmer. Pressure variations sometimes failed to affect the skin temperature of the cold extremity, but as soon as vasoconstrictor tone was diminished slightly, skin temperature rose conspicuously in the treated extremity. The vasodilator response to warming one forearm appeared earlier, and was more complete, in the extremity exposed to external pressure changes. The studies were then extended to include patients with peripheral vascular disease advanced to the stage when a rise of skin temperature could no longer be induced by abolishing vasoconstrictor tone. In these patients, alternate suction and pressure increased blood flow even though pronounced organic obstruction was present (Landis and Gibbon<sup>4</sup>). It was suggested that this procedure might help to alleviate the manifestations of the ischemia ordinarily observed in patients suffering with obliterative structural disease of the arteries.

Reid and Herrmann<sup>15</sup> simultaneously studied the effects of treating patients by applying intermittent negative pressure alone to the extremity, according to Bier's method. In their first report (1933) they advocated the following procedure: "The air is slowly withdrawn from the chamber so that about 2 minutes are required

to reduce the pressure within the chamber to 70 mm.Hg of negative pressure. . . . The negative pressure of 70 mm. is allowed to act upon the vessels of the extremity for 1 minute and then the pressure is slowly *increased* until atmospheric pressure is reached. This phase of treatment should also be done in about 2 minutes. The entire cycle will then be completed in about 5 minutes. Five to 10 such cycles constitute 1 treatment." Reid and Herrmann advised against the use of intermittent positive pressure because "serious secondary arterial thromboses" were produced in 3 cases. In a 5-minute cycle the prolonged period (2 minutes) of positive pressure might well be injurious since the pallor of the skin, even after a few seconds of positive pressure, indicates that the skin becomes relatively, if not completely, ischemic.

Landis and Gibbon,<sup>4</sup> in using +80 mm.Hg for 5 seconds, observed no deleterious effects in normal subjects or in patients with peripheral vascular disease. Nor have any injurious effects been observed in the studies reported in this paper. Herrmann and Reid found also that a negative pressure of more than 100 mm.Hg was apt to produce hemorrhages into the skin. It seems likely that this was due also to the long period (2 minutes) of suction and to incomplete emptying of the veins during the period when atmospheric pressure prevails. Both in normal subjects and in patients (Landis and Gibbon<sup>4</sup>), suction amounting to -120 mm.Hg for periods of 25 seconds did not produce visible cutaneous hemorrhages. In the studies reported in this paper no hemorrhages were observed presumably because the peripheral vessels were well emptied between suction periods by applying positive pressure (60 to 80 mm.Hg) for 5 seconds.

In a more recent publication, Herrmann and Reid<sup>16</sup> describe a commercially available unit which they have arranged for the use of suction and pressure up to 100 mm.Hg. They recommend that the alternation of suction and pressure be made at the rate of 2 or more complete cycles per minute instead of 1 cycle in 5 minutes—their original interval. They recommend a negative pressure of 80 mm.Hg and a positive pressure of 20 to 40 mm.Hg, the latter being required to empty the veins completely, particularly in thromboangiitis obliterans. Elevating the limb aids the return of venous blood and is more feasible with a glass container such as they use than with the heavier aluminum box used in the observations reported by us. As in the original Bier technique, however, the pressure variations are introduced slowly, the whole cycle being required for the *gradual* change from -80 to +40 mm.Hg. The average negative pressure is, therefore, considerably less than 80 mm.Hg, which represents merely the peak of negative pressure reached. In the studies reported here, -120 mm.Hg indicates the negative pressure during the whole of the 25-second period. The change from positive to negative pressure is made rapidly (during 3 seconds) to avoid the loss of mechanical efficiency which must

accompany the slower changes in pressure. This procedure requires a larger pump, a more powerful motor and larger tubing between the pump and the treatment apparatus. There is no way at present of deciding which procedure will provide the best practical results. Rapid and greater changes of pressure modify skin color more strikingly than do slower changes. Other things being equal, the flow of blood should be increased to a greater degree by changing pressure suddenly since the average negative pressure is greater.

Most of the patients whose course during suction and pressure therapy is described in this paper had been treated conservatively by the usual methods without success. The apparent benefit derived is, therefore, more significant than it would have been if unselected cases had been treated. The rise in skin temperature (Landis<sup>5</sup>), the diminution of rest pain and the healing of previously indolent ulcers indicate that alternate suction and pressure increases the blood flow at least temporarily. At the present time it is impossible to do more than speculate upon the permanence of this improvement. Complete and lasting recovery depends upon the development of adequate collateral circulation.\* Sufficient time has not elapsed to determine to what extent increased blood flow depends upon the continued use of pressure variations. In some patients, collateral circulation seems to develop slowly during and after treatment (Landis,<sup>5</sup> Table 4, Cases 22, 23, 24, 25). The majority of the patients who were studied with reference to their vasodilator response before and after brief periods of treatment showed no significant change. This means only that the increase in the rate of blood flow was not sufficient to be measured objectively by recording skin temperatures during vasodilatation. It is conceivable that temporary clinical improvement may occur without change in the vasodilator response which is, at best, a rather crude test for measuring small changes in blood flow.

\* The importance of this factor is emphasized by the recurrences since observed in Cases 3, 12 and 18. These 3 patients showed no increase in vasodilator response during or after suction or pressure therapy and received no significant amount of therapy after they were discharged from the hospital.

In 1 instance (Case 3) a necrotic lesion of the great toe appeared 6 months later and advanced slowly in spite of suction and pressure therapy. Amputation of the leg above the knee revealed marked sclerosis of the femoral artery. In Case 12 gangrene of the toe appeared 4 months after the patient was discharged from the hospital. Ascending infection contraindicated suction and pressure and led finally to amputation above the knee. Case 18 suffered from the subacute form of thromboangiitis obliterans which had already required amputation of 3 digits in the course of 2 years. The patient returned 1 year after the second admission, described in Table 3, with a deep ulcer at the base of the fifth digit. Involvement of an interphalangeal joint and osteomyelitis of a phalanx contraindicated suction and pressure therapy. The fifth toe was amputated in January, 1935, local heat, vasodilator drugs and suction and pressure being used to aid healing of the wound.

In these 3 cases collateral circulation obviously did not develop to any significant degree and clinical improvement was only temporary. Whether or not continued treatment after the patients were discharged would have modified the final result is not known.



*Contraindications.* Contraindications to the use of suction and pressure can be given at this time on theoretical grounds only, since the number of cases treated is far too small to permit generalization. Pressure variations cannot be used indiscriminately or without careful medical supervision. There must be no active or spreading cellulitis in the limb. In 2 patients, both diabetics, a doubtfully indolent process was aggravated by the first few hours of treatment and amputation was probably hastened rather than delayed. Before suction and pressure is used it should be carefully ascertained that encapsulated pus is not present. Infective material might easily be massaged into the lymphatics more rapidly during pressure variations. Osteomyelitis, however slight, makes it unlikely that complete healing of cutaneous lesions can be obtained as long as drainage from beneath continues. When large masses of tissue are actually gangrenous, or sloughing, only temporary relief has so far been observed.

*Indications.* The procedure seems to be worthy of clinical trial, particularly for patients in whom treatment with ordinary conservative measures is ineffectual. Evidence is accumulating to show that if patients can be aided temporarily during episodes of pain or ulceration, time is gained for the natural development of adequate collateral blood flow and mutilating operations can often be avoided. In this connection alternate negative and positive pressure therapy can be of service even to those patients whose peripheral arteries have lost their power of dilatation owing to advanced obliterative arterial disease. Suction and pressure therapy should not displace but can be added to other conservative measures.

*Summary.* The extremities of 29 patients suffering from advanced peripheral vascular disease were exposed to alternate suction ( $-80$  to  $-120$  mm.Hg) and pressure ( $+40$  to  $+80$  mm.Hg) for 25 and 5 seconds, respectively. These pressure variations were used for periods of 1 to 2 hours, at first once or twice daily, then 3 times weekly and finally, as symptoms diminished, once weekly.

Cyanosis usually diminished; symptomatic improvement was sometimes observed, however, without significant change in skin color.

The rest pain of ischemia was usually abolished during actual use of suction and pressure and gradually became less severe in the intervals between exposure to pressure variations. Lasting relief of pain was not observed in the presence of deeply extending gangrene or large sloughs.

Ulcers, enlarging or indolent under ordinary conservative treatment, usually began to heal soon after suction and pressure therapy was instituted.

Intermittent claudication became, in general, milder and exercise tolerance was slightly, but definitely, increased.

Suction and pressure therapy was of no definite, lasting service

in patients with osteomyelitis, deeply extending gangrene or large sloughs.

This form of therapy must be applied with caution, small pressure changes being used at first. The presence of acute spreading infection or encapsulated pus must be definitely ruled out before pressure variations are used.

Suction and pressure therapy, if carefully applied, appears to be worthy of clinical trial in the treatment of peripheral vascular disease even when organic obstruction has advanced to the point where arterial blood flow can no longer be increased by vasodilatation. The method may be of service by increasing local blood flow temporarily during episodes of pain or ulceration so that time is gained for the development of adequate collateral blood flow.

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### A TENTATIVE WORKING CLASSIFICATION TO FACILITATE THE TREATMENT OF PULMONARY TUBERCULOSIS.\*

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In the following classification we have divided all patients into two races, white and negro, and each of them into two groups, the minimal and the advanced. The patients with advanced disease

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have been further subdivided on the basis of the type of the predominating disease into the proliferative and the exudative. Under each of these we have discussed the moderately advanced and the far-advanced stages. These in turn have been separated into those with and those without cavity formation and whether or not the disease extended below the third rib. Finally we have attempted to outline the treatment of the patients according as to whether or not the disease was retrogressing, stationary or advancing. The surgical procedures are arranged in the order in which we recommend them.

It has long been considered a doubtful procedure to suggest any form of surgical intervention for patients in the truly minimal stage of pulmonary tuberculosis. In this stage the slight infiltration does not extend below the level of the second chondrosternal junction if unilateral or below the level of the clavicles if bilateral. Cavitation is, of course, never present. The results of treatment in such patients at the Trudeau Sanatorium reveal that at the end of 15 years 92% are alive. It is doubtful if the results of treatment in any class of patients with pulmonary tuberculosis will be found to be much better than this. Accordingly it seems safe to watch such patients and refilm them from time to time. If the second film shows a definite increase of the disease, the plan of immediate treatment depends upon what the patient has been doing up to this time. If he has been active, he should be put at rest and carefully watched. If he has been on strict rest, active surgical interference at once may be considered, particularly when time or finances are pressing or urgent. In such patients, especially those where there is some indication of pulmonary contraction (the trachea drawn toward the diseased side, the diaphragm elevated, the mediastinum shifted), a temporary phrenic operation may be all that is required to bring about recovery. Artificial pneumothorax may be also considered, as the favorable results following this operation in the early stages of the disease in negroes suggests that it may be safely applied to other races.

Patients in the advanced stage of pulmonary tuberculosis should be grouped, we believe, according to the type of the predominating disease, into the proliferative and exudative groups. This, at times, is not a simple matter and the doubtful cases may be placed in the exudative group and watched more carefully. In each of these two groups the division into moderately and far-advanced stages should be followed, for they are important in determining the form of treatment required. Again it is necessary for the same reason to separate those with, from those without cavitation. The presence of a cavity automatically places the patient in the advanced group and any cavity with a diameter over 4 cm. falls once more automatically into the far-advanced group. Patients in the proliferative, moderately advanced group without cavitation can usually be

safely treated somewhat longer without resort to surgical interference. If the disease improves, surgical treatment is not indicated nor is it necessary in patients in a stationary condition though they need more careful watching. If the disease advances in spite of other forms of treatment, surgical interference is required.

As a pulmonary cavity can practically never heal until its walls approximate, as a wet-walled cavity usually gives off more or less numerous tubercle bacilli which constitute a threat to the remainder of the lung as well as to the opposite side, it is at once apparent that such an approximation of the walls is highly desirable as soon as possible. As soon as the disease in any case of pulmonary tuberculosis extends below the third rib (which usually implies that it has passed beyond the extent of a single lobe) the disease becomes much more serious. This is taken into account in patients with cavitation. In all patients retrogression of the disease is a hopeful sign but too much must not be based upon it when it is not associated with a very definite decrease in the size of the cavity. Hence surgical treatment may be required for a persistent unchanging cavity. In stationary disease lasting over 2 or 3 months, if symptoms or tubercle bacilli increase, or in progressive disease, surgical treatment is indicated. When the disease extends below the third rib, active surgical treatment is demanded earlier and upon slighter symptoms. The patient in the far-advanced proliferative stage without cavity usually requires no surgical treatment except for displacement of viscera, when a phrenic operation may relieve the situation. We can picture a patient in whom a marked contraction, similar to that following an organizing atelectasis, may require an artificial pneumothorax. A patient with a proliferative far-advanced stage of the disease with cavitation may demand surgical treatment even when the disease is retrogressing.

All patients with the exudative type of disease should be considered to be in a more serious, a more rapidly changing, a more acute condition. In a certain number the condition improves very rapidly but in others it progresses just as rapidly. Hence it is highly important to watch these patients more closely than those with proliferative disease. Cavities frequently appear with startling rapidity and may enlarge very suddenly. On account of the rapid changes that often occur in patients between the ages of 12 and 19, especially in girls, it is well to place such patients under this head. For similar reasons all negro patients fall into this group. In this group artificial pneumothorax is the operation of choice. The phrenic operation is often of little aid. In certain acute unilateral cases when the patients are in good general condition, having been ill and confined to bed but a short time, when artificial pneumothorax cannot be produced and when the phrenic operation has been of no avail, thoracoplasty may be considered. In many of such patients the chances of recovery are very slim without some form

# A TENTATIVE WORKING CLASSIFICATION TO FACILITATE THE TREATMENT OF PULMONARY TUBERCULOSIS.

## THE WHITE RACE.

Patients in *Minimal Stage*.

A. Surgical treatment unnecessary (only 8% dead at end of 15 years). Watch and refill.

B. Second film shows definite increase of disease:

1. Active life at time of second film has been doing up to this time.
2. Active treatment at time of second film with increase indicates Rest (postural, etc.).
  1. Phrenic operation temporary.
  2. Artificial pneumothorax.

Patients in *Advanced Stages*.

Type of predominating disease.

## I. PROLIFERATIVE.

Patients in *Moderately-advanced Stage*.

*Without Cavity*

A. Retrogressing disease:

No surgical treatment; watch and refill.

B. Stationary disease:

Watch carefully for 2 or 3 months; symptoms determine treatment. If persistent, temporary phrenic operation too soon rather than too late.

C. Progressing disease:

If this occurs in spite of Rest Treatment, active surgical treatment is suggested at once regardless of symptoms.

1. Phrenic operation—with more limited lesion.
2. Artificial pneumothorax.
3. Thoracoplasty questionable.

*With Cavity* (never over 4 cm. in diameter)

After the disease reaches a certain stage cavitation is the first step toward healing and automatically advances the case into the moderately or far-advanced group.

1. Disease not extending below third rib

A. Retrogressing disease:

No immediate surgical treatment. Watch. Refill. Persistent cavity except possibly in good chronic suggest surgical treatment.

B. Stationary disease (unusual):  
If symptoms slight or absent watch carefully for 2 or 3 months. If symptoms and or tubercle bacilli increase active surgical treatment suggested. (See under Progressing disease.)

Progressing disease:

Demands active surgical treatment.

1. Phrenic operation (with or without scalenotomy) with smaller, earlier, thin-walled cavities.
  2. Artificial pneumothorax.
  3. Thoracoplasty.
2. Disease extending below the third rib or ribs:  
More dangerous.  
Active surgical treatment demanded earlier and on slighter indication.

Patients in *Far-advanced* Stage  
(Bilateral, more than one lung in extent, fibroid.)

#### Without Cavity

Usually requires no surgical treatment except for displacement of visceræ.

Phrenic operation?

#### With Cavity

Retrgressive, Stationary, or Progressive suggest surgical treatment, depending upon symptoms and tubercle bacilli.

1. Phrenic operation alone?
2. Artificial pneumothorax (always attempt before thoracoplasty).
3. Thoracoplasty (favorable type for).

## II. EXUDATIVE.

More serious; usually more acute; usually associated with cavity. Type of disease usually determines type of cavity. All female teen-age patients to be treated as if exudative.

#### Patients in *Far-advanced* Stage

- A. Retrgressive disease:
1. Artificial pneumothorax.
  2. Phrenic operation?

B. Stationary disease:  
Non-existent.

- C. Progressive disease:
1. Artificial pneumothorax.
  2. Phrenic operation?

#### Patients in *Moderately-advanced* Stage

A. Retrgressive disease:  
Highly dangerous on account of sudden changes. Watch most carefully. Roentgen-ray by weeks. Symptoms very important.

B. Stationary disease:  
Almost non-existent. Marked unchanging symptoms demand immediate, active surgical treatment.

1. Artificial pneumothorax (operation of choice).
2. Phrenic operation?
3. Thoracoplasty if unilateral (when artificial pneumothorax and phrenic fail).
4. Pneumectomy? (possibly also following unsuccessful thoracoplasty; theor.).

C. Progressive disease:

Active surgical treatment demanded at once.

1. Artificial pneumothorax (method of choice).
2. Phrenic operation?
3. Thoracoplasty (only if strictly unilateral on account of danger of contralateral spread).

#### THE NEGRO RACE.

##### I. Patients in the *Minimal* Stage

- A. Rest in bed one month.
- B. Second film in one month shows increase:  
Surgical treatment indicated:

1. Phrenic operation?
2. Artificial pneumothorax (operation of choice).

##### II. Patients in *Advanced* Stage

Treat as if all came under *Exudative* group (of whites).

of surgical intervention. As artificial pneumothorax has often so greatly increased the chances of recovery in such patients, it seems justifiable, if pneumothorax cannot be produced, to resort to thoracoplasty, in hopes that extension to the opposite lung may be prevented and that the collapse produced may act in a way similar to that brought about by artificial pneumothorax. A desperate condition demands taking considerable chances. Even when the disease in the exudative cases is retrogressing, and more particularly when it is apparently stationary, surgical measures must be thought of. While this holds for the moderately advanced stage, the only hope for the far-advanced group lies in artificial pneumothorax. Intrapleural pneumolysis must be considered in all cases of incomplete artificial pneumothorax.

This tentative working classification is not intended for the surgeon with experience in thoracic surgery nor for the specialist with long training, but rather for the physician either in the sanatorium or on the outside, who needs assistance in deciding about the treatment for some of his patients.

### SUSCEPTIBILITY TO TUBERCULOSIS: RACE OR ENERGY LEVEL?\*

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IN dealing, as physicians, with the tuberculosis problem we have been so intent on the matter of early diagnosis and treatment of the individual patient that we have too often failed to see the larger aspects of the disease in its general relationship to man. Steady decline in its death rate has largely resulted from improvement in the hygienic care of the active cases to prevent spread of infection. There remain, however, important underlying factors affecting susceptibility and resistance to the infection which deserve careful study.

Man has not everywhere the same resistance to tuberculosis. We have long recognized this fact in contrasting the severity of the disease in the negro with its less deadly course in the white race. We also are aware of the loss of resistance that accompanies states of low vitality from whatever cause (worry, grief, poorly controlled diabetes, malnutrition, overwork, exhaustion, etc.) and of the curative value of building up the general physical state of the body.

\* All mortality figures in this article were obtained from annual statistics as issued by the Federal Government. Conception figures were derived from statistics of live births by dating back 9 months and 10 days. For a description of the method of estimating storminess, or temperature variability, see *Am. J. Hyg.*, 15, 573, 1932.

There are, however, still other factors affecting the whole population which exert a marked influence on the general resistance to tuberculosis, factors that in the main affect the energy level of existence and the physical vigor of man. It is this aspect of the problem which will be taken up in the following paragraphs.

We have in various papers<sup>1</sup> shown how bodily energy depends on the stimulating character of the environment, with temperature level and variability as perhaps the most important factors. Metabolic diseases are found to vary in frequency and severity in direct proportion to the degree of this climatic stimulation, while for certain infectious diseases (acute nephritis and acute appendicitis) an inverse relationship was found. Where the climatic drive produces most severe metabolic disturbances, there do we find the general resistance to infections highest, while in the Gulf States, where diabetes and toxic goiter are of little importance, resistance to infection is low. With the wide and frequent storm changes of

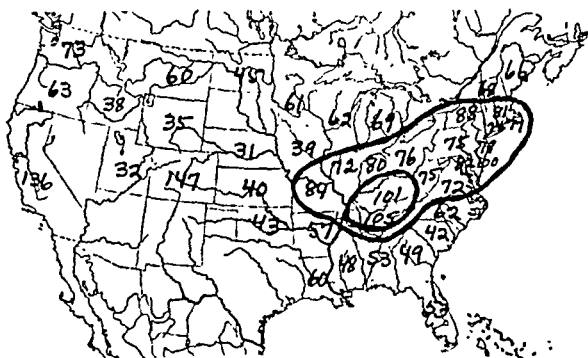


FIG. 1.—Death rate from tuberculosis (all forms) per 100,000 estimated population, by states. White race only—annual average, 1924-1928.

the Northern States, man must endure much more frequent infectious attacks, especially in the respiratory tract, but his high vitality counterbalances this frequency of attacks. Were the people of the Gulf States suddenly to be subjected to the weather fluctuations of a northern stormy season, the respiratory disease death rate would be terrific.

Let us now look into the climatic relationships of tuberculosis. There are first presented the state and city white death rates for the disease over a 5-year period (Figs. 1 and 2). The high rates for the Southwest (California, Colorado, Arizona and New Mexico) should be disregarded, as they probably represent migration to this area of tuberculosis individuals from other states. Otherwise, the highest state rates for the white population are found in Tennessee and Kentucky, with the secondary high zone covering most of the states to the north and east. Throughout the Western Plains the state rates are low, while along the Gulf they are only slightly higher.



Because state rates for tuberculosis are so often influenced by the distribution of the population between city and country, rates for large cities were calculated and are presented in Fig. 2. Here one sees a V-shaped arrangement of the high rates, with the apex at New Orleans and one arm covering the northeastern area that shows the high state rates. The other arm extends northwestward up the plains into the Canadian provinces. This is quite similar to the graphs of acute appendicitis attacks and deaths and to puerperal sepsis deaths. In general, this V represents the course of our cold polar waves as they sweep down out of Canada, pass down the Western Plains to, or near to, Texas, and then reverse their direction to pass back up the Mississippi and Ohio Valleys on their way to the mouth of the St. Lawrence.

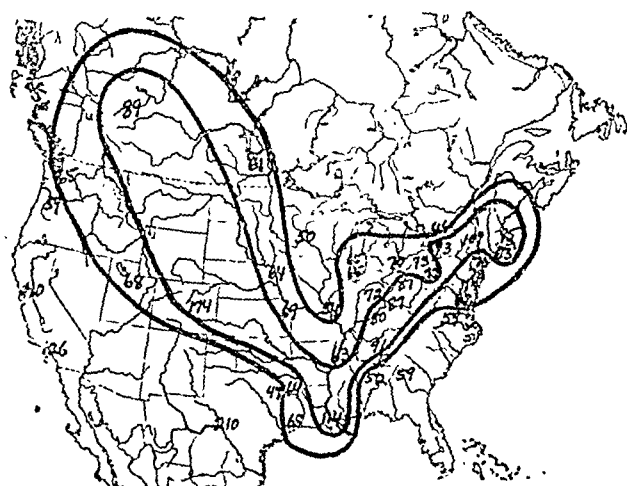


FIG. 2.—Death rate from tuberculosis (all forms) per 100,000 estimated population, in large cities. White race only—annual average, 1924-1928.

Negro rates, while everywhere roughly 3 to 5 times higher than the white, show a steady increase on passing northward from the Gulf. Note in Table 1 the steady increase from Georgia up to Maryland and from Alabama up to Kentucky. They also show a diminution westward from the Mississippi River. The Ohio Valley seems to be particularly bad for tuberculosis (see Table 1 for negro rates by states and cities). A study of reported case incidence and case fatality over the country is now being made, preliminary figures indicating a much lower case fatality rate in the northern stormy area than in the South.

In order to obtain a closer insight into the disease and its general characteristics, an analysis was made of the records of the Hamilton County Tuberculosis Sanatorium for the past 25 years. Cases were selected where a definite month for the onset of symptoms was ascertained and recorded, and the statistics were tabulated on the

basis of color, state of birth, duration of disease and time of onset. Fig. 3 shows the curve of frequency of onsets throughout the 12 months, based on 3179 cases. For comparison is given the graph of temperature variability, or storminess, for 8 northern cities (Boston, New York, Baltimore, Cincinnati, St. Louis, Minneapolis, Chicago and Cleveland) which would also hold fairly well for Cincinnati alone. Here is seen the close parallelism between storminess and tuberculosis onsets throughout the year, both reaching a peak in January and the low point of the year in July and August. The general curve of all respiratory infections, if plotted, would also follow much this same course, as would an inverted curve for the hours of sunshine.

TABLE 1.—DEATHS FROM TUBERCULOSIS (ALL FORMS) PER 100,000 ESTIMATED COLORED POPULATION. ANNUAL AVERAGE, 1924-1928.

*States.*

Maryland . . . . .	269	Tennessee . . . . .	295
Virginia . . . . .	194	Alabama . . . . .	165
North Carolina . . . . .	169	Mississippi . . . . .	156
South Carolina . . . . .	144	Louisiana . . . . .	177
Georgia . . . . .	142	Arkansas . . . . .	146
Florida . . . . .	151	Oklahoma . . . . .	146
Kentucky . . . . .	270		

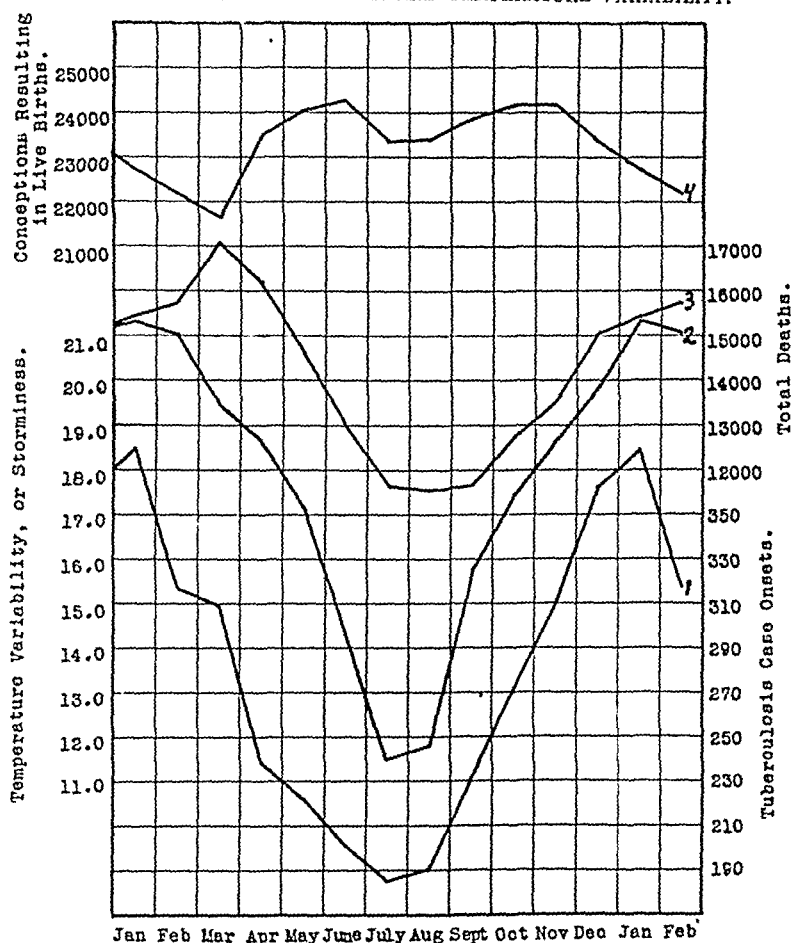
*Cities.*

Los Angeles . . . . .	494	Washington . . . . .	283
Cincinnati . . . . .	456	Indianapolis . . . . .	260
Cleveland . . . . .	432	Memphis . . . . .	244
Kansas City, Mo. . . . .	366	Birmingham . . . . .	242
Chicago . . . . .	355	Pittsburgh . . . . .	231
Detroit . . . . .	321	Atlanta . . . . .	224
New Orleans . . . . .	306	Dallas . . . . .	221
Nashville . . . . .	300	Richmond . . . . .	215
St. Louis . . . . .	299	Louisville . . . . .	210
New York . . . . .	299	Fort Worth . . . . .	170
Philadelphia . . . . .	297	Houston . . . . .	124
Baltimore . . . . .	291		

This seasonal difference in frequency of onsets, while it follows storminess very closely, does not coincide exactly with variations in general vitality in the population. In Fig. 3 are also shown the month by month rates for conceptions resulting in live births and for deaths for the 8 cities mentioned in the preceding paragraph. These two rates are functions of general vitality and are usually mirror images of one another, although in this instance the conceptions show a depression for the July and August heat as the mean monthly temperature rises above 70° F.<sup>2</sup> The general death rate and tuberculosis onsets are both lowest through mid-summer and rise steadily through the fall and early winter. The deaths continue to rise through March, however, while the decline in tuberculosis begins in February. The precipitous decline in case onsets comes in April, however, as the general death rate turns downward and the conception rate shows a sharp rise.

In view of the marked tendency for the disease to begin producing symptoms during the colder, more stormy months, it seemed advisable to see whether it was less deadly in summer than in winter. To this end cases were grouped according to month of onset and

FIG. 3.—SEASONAL VARIATIONS IN TUBERCULOSIS ONSETS IN RELATION TO CONCEPTIONS, TOTAL DEATHS AND TEMPERATURE VARIABILITY.

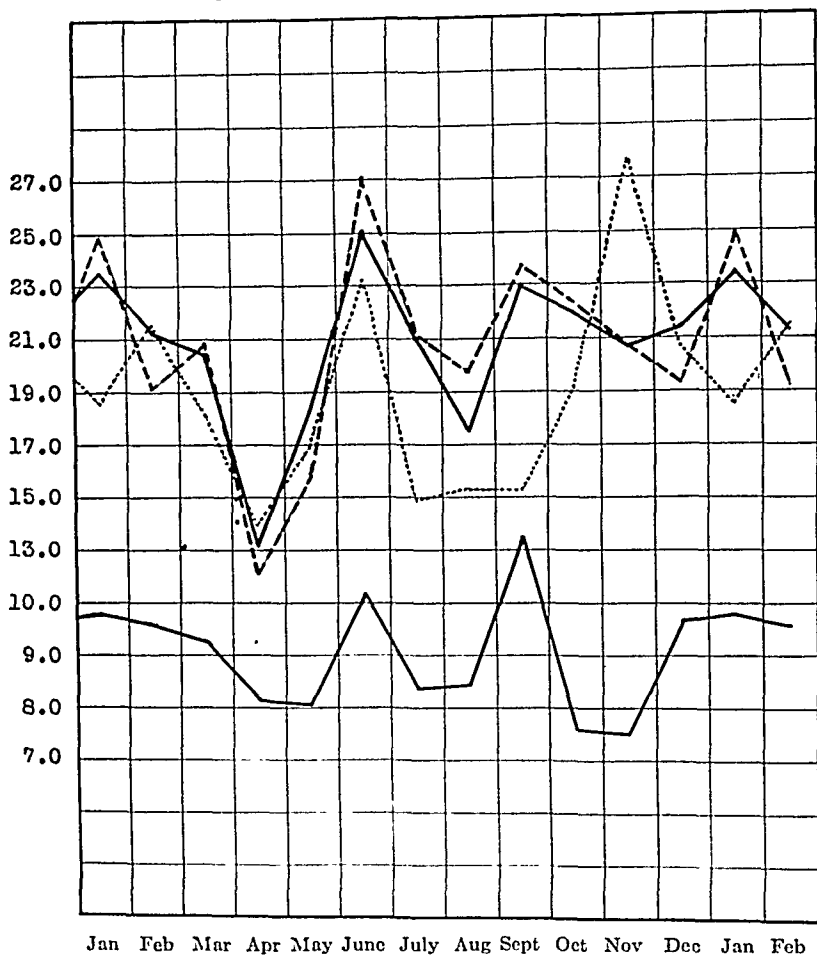


1, Tuberculosis onsets are for patients who died at the Hamilton County Tuberculosis Sanatorium from 1909 to 1934. 2, Temperature variability curve represents mean monthly values for the past 60 years for the 8 stations named in text. 3, Curve for total deaths represents 5-year average of total deaths, month by month, for same 8 cities from 1924 to 1928. 4, Conceptions resulting in live births also represent 5-year average.

months of duration between onset and death. In Fig. 4 are graphed the mean durations of the disease in months according to the time of year it started. All Ohio-born white cases from 1909 to 1933 are shown in the upper solid graph. In the dashed graph are shown the findings for the part of these white cases coming on from 1909

to 1920, inclusive, while the cases arising since 1920 are presented in the dotted graph. In the lower solid graph were included the findings from negro patients whose birthplace lay in Alabama, Georgia, South or North Carolina.

FIG. 4.—MEAN DURATION (IN MONTHS) OF TUBERCULOSIS IN CINCINNATI ACCORDING TO MONTH OF ONSET AND BIRTHPLACE.



Upper solid graph represents white patients born in Ohio who contracted the disease from 1909 to 1934. Dashed graph represents Ohio-born white cases with onset from 1909 to 1920, inclusive. Dotted graph represents Ohio-born white cases with onsets since 1920. Lower solid graph represents all negro cases with birthplace in Alabama, Georgia, South or North Carolina.

Certain striking features of these 4 graphs stand out clearly. First is the short duration of the disease in cases with onset in April. All groups, black and white, show this rapid course of the disease from an April beginning. Next is seen the uniform high peak in June for all groups, cases starting in June being in general of longer duration. July and August appear less favorable, while

in September the mean duration again shows a marked rise in all but one group. October and November are again characterized by shorter duration from onset to death, but through December and January the tendency seems to be for a slower course.

That these findings for two different time periods with Ohio-born white patients, and for the Southern-born negroes, should show such agreement throughout the year must indicate a definite trend in the disease course, depending on the month of onset. It must be significant, for instance, that the sharp lengthening in disease duration to its June peak should coincide with the year's highest conception rate. Likewise it is probably not by chance that cases of the disease beginning in July and August, when conceptions are depressed by the summer heat, should pursue a more rapidly fatal course. In the early fall, conceptions turn upward as the disease duration again lengthens. Then in late fall, the trends are reversed. Most striking of all, however, is the fall in resistance to tuberculosis that reaches its crisis in April. Persons contracting the disease in Ohio in April would seem to be subjected to distinctly greater hazards than those who become ill in June.

TABLE 2.—MEAN DURATION (IN MONTHS) OF TUBERCULOSIS ACCORDING TO BIRTH-PLACE.\*

Birthplace.	Color.	No. of cases.	Mean duration, mos.
Ohio	White	912	22.27 $\pm$ 0.66
Other Northern States and Canada	White	164	24.65 $\pm$ 1.50
Kentucky	White	217	21.34 $\pm$ 1.20
Tennessee	White	40	22.83 $\pm$ 2.65
Miss., La., Ark., Texas, Okla.	White	16	20.13 $\pm$ 4.62
Md., D. C., Va., W. Va.	White	36	15.00 $\pm$ 1.65
N.C., S.C., Ga., Fla., Ala.	White	19	11.82 $\pm$ 1.84
Central Europe and Great Britain	White	175	20.60 $\pm$ 1.21
Ireland	White	39	21.96 $\pm$ 2.74
Eastern Europe	White	51	19.44 $\pm$ 1.69
Mediterranean countries	White	50	11.74 $\pm$ 1.03
Ohio	Black	168	16.84 $\pm$ 1.64
Other Northern States	Black	41	11.50 $\pm$ 1.01
Kentucky	Black	298	11.21 $\pm$ 0.45
Tennessee	Black	88	10.10 $\pm$ 0.85
Miss., La., Ark., Texas, Okla.	Black	57	12.24 $\pm$ 1.61
Md., D. C., Va., W. Va.	Black	86	10.91 $\pm$ 0.72
North and South Carolina	Black	117	9.40 $\pm$ 0.48
Alabama	Black	177	9.09 $\pm$ 0.46
Georgia	Black	204	9.37 $\pm$ 0.41

\* Taken from 2955 records of patients dying at the Hamilton County Tuberculosis Sanatorium.

It will be noted from Fig. 4 that the Southern-born negro patients exhibit always a shorter duration of the disease than do the Ohio whites. To investigate this point more thoroughly, cases were grouped on the basis of place of birth, color and duration of disease. The mean duration, in months, of the disease in the different groups is shown in Table 2. Here, again, certain facts stand out. The

disease in negroes everywhere shows a significantly shorter course than is seen in white patients from the same region. For both negro and white patients, who contract the disease and die in Cincinnati, there is a strong tendency for the duration to be shorter the farther south the birthplace of the patient. Thus for negroes, those born in Alabama succumb most rapidly, those from Georgia next, then the Carolinas, Tennessee, the Virginias and Maryland, Kentucky and, finally, those born in Ohio. The Ohio-born group lasts almost twice as long as do the native Alabamans. Data for white patients show much the same picture, although fewer cases were available. Ohio-born whites, however, last almost twice as long as do those from the Carolinas, Georgia, Florida and Alabama. The differences between white natives from Ohio, Kentucky and Tennessee are not of importance.

One group shown in the table deserves special mention. Migrants, both white and black, born in the South from Mississippi westward seem to show a much greater resistance to tuberculosis than do Southerners from the more eastern Gulf States. In them the duration of the disease is not far below that shown by natives of Ohio. This fits in with the fall in both colored and white state tuberculosis death rates from the Mississippi River westward (Fig. 1 and Table 1). Just what relation this greater resistance to the ravages of tuberculosis in the lower plains states bears to the storm stimulation they receive is a question demanding further study. The great bodily vigor in this region is quite as evident in animal life as in man, however, for here cattle and hogs thrive almost as well as in the North, quite in contrast to the other southern states.

Of still further interest is the way the data on European migrants bear out the findings of the American-born patients. The patients who were born in the British Isles and Central Europe showed a survival time close to that of the Ohio-born. With a birthplace farther eastward, in Russia, Poland, Roumania and Finland, the patients were slightly less resistant, fitting in with the lessened climatic vigor of their native land. But most striking is the duration of only 11.7 months for patients from the Mediterranean countries, a figure almost identical with that found for white migrants from our southeastern states. These differences between migrants from the British Isles and Central Europe and from the Mediterranean countries cannot but be of significance, since they coincide so closely with differences observed in American-born migrants. The conclusion would seem justified that ability to withstand the spread of tuberculosis infection is in some manner related to climatic vigor, quite independent of race or nationality. From other recent studies it would seem most likely that the basic factor at play is the energy level, which in turn is definitely dependent on the degree of climatic drive imposed on the population, especially throughout childhood and adolescence.

Just one further point must be included in this article. It bears on the conclusions given in the last preceding paragraph. When we speak of racial susceptibility to tuberculosis, we commonly think of the negro as having the least resistance to the disease. Mortality statistics, however, show that American residents of another race have over twice the tuberculosis death rate exhibited by the negroes. The Chinese in this country, as shown in Table 3, have the highest rate of all groups listed. Although tuberculosis in China is a serious disease, it does not there run such a rapidly fatal course as we see in the negroes of our northern states. China is a land of stable climate, with even fewer storms than our eastern Gulf States have, so perhaps it is to be expected that they pay a heavy price for migration into our stormy northern area. The mental remark of many readers to this mention of the Chinese will doubtless be that their habits of living account for their high rate; but they fit too well into the general disease picture for such a simple explanation to suffice.

TABLE 3.—DEATHS FROM TUBERCULOSIS (ALL FORMS) BY RACE, IN U. S. A. PER 100,000 ESTIMATED POPULATION.

	Negroes.	Indians.	Chinese.	Japanese.
1920 . . . . .	239.0	391.6	526.3	221.4
1929 . . . . .	185.7	331.8	358.6	152.0
Percentage reduction over 9-year period . . . . .	22.3	15.3	31.9	31.3

One often hears the remark that the high tuberculosis death rate among the Indians is probably due to the relative newness of the disease with them, and that perhaps somewhat the same situation holds for the negroes. But here are the Chinese in this country with the highest rate of all, even though in their own country tuberculosis has long formed no mean problem. It would be well worth while to look further into the tuberculosis situation among Indians under different climatic conditions to see if they too show the same relationship to climatic stimulation as do the black and white races.

*General Summary.* Certain facts stand out from the data available on tuberculosis. Although the disease is more prevalent and causes more deaths in the cooler more stormy regions, still we find among such populations the highest resistance to its progress. The mean duration of the disease among Ohio-born whites was found to be 22.27 months, while Southern-born whites lasted only 11.82 months. Ohio-born negroes lasted 16.84 months, but Alabama-born negroes only 9.09 months. Likewise among European migrants, those from Central Europe lasted 20.6 months, but those from Mediterranean countries only 11.74 months. These differences in ability to withstand the progress of the disease are too great to be of chance occurrence. They also are significantly related to

the level of climatic stimulation, for the Mediterranean countries of Europe are quite similar to our Gulf States in this respect, and Central Europe only slightly below our northern storm belt. It is also of significance that people from the only part of the South which receives a fair number of storms—westward from the Mississippi River—should show a resistance to tuberculosis almost as great as that of Northerners.

It should be remembered that the data presented in this paper are based on case histories of patients that *died* of tuberculosis. Could it have been possible to include data as to the duration of the disease in patients yet living, the difference between the Northern and Southern born would most probably have been even greater. Anatomic evidence has also recently been set forth<sup>3</sup> to show a more chronic course of the disease in the Northerner, either white or black, with better tissue response to the infection. All factors considered, resistance to tuberculosis does seem to be closely related to metabolic level, this in turn being determined by the intensity of climatic stimulation.

In practically all tropical and subtropical regions where tuberculosis has been studied, the natives have been found to possess very little resistance to the disease. In adults it usually pursues a rapid course and is of the childhood type. Opie<sup>4</sup> emphasized this point for Jamaica negroes, contrasting a duration for the disease in them of about 9 months with one of 28 months among Philadelphia white patients. Colored troops from Africa, imported into Europe during the World War, showed an amazing lack of resistance to tuberculosis, for in them it became an acute infection. The longest duration of symptoms seen was only 3 months.<sup>5</sup> Numerous references<sup>3</sup> have been made to this extremely low resistance of tropical natives, and much speculation has taken place as to the reasons for it. In view of the findings reported on the previous pages, it would seem that the low metabolic and energy level of these people may well be the chief reason for their lack of resistance. Broadening the study to include other infectious diseases will probably clinch the point, for if people in regions of stagnant heat show a lessened ability to combat all other infections, then we must accept this as the basis for differences in tuberculosis.

In a very large number of the case histories investigated in this study, the onset of symptoms dated sharply from attacks of acute respiratory infection. This, together with the fact that the curve of onset frequency for tuberculosis is similar to that for other respiratory infections, would seem to link them closely together. In view of this it would seem advisable that particular care be exercised in tuberculosis hospitals and sanatoria to avoid all forms of respiratory infection. From our present-day knowledge, this would seem to mean the avoidance of our severe storm fluctuations in atmospheric conditions during the more changeable months, particularly those



of the spring. Likewise the more rapid course of the disease from an onset in the mid-summer heat indicates the advisability of protecting patients who already have the disease from the debilitating effects of summer heat waves. In other words, the indication seems plain that, for most efficient care of tuberculosis patients, hospitals and sanatoria should be conditioned for year-round control of their indoor atmosphere.

One more point should be stressed in this paper. Too great emphasis cannot be placed on the dangers encountered by people who migrate from regions of low climatic vigor into our northern storm belt where climatic stimulation is probably the most intense to be found anywhere on earth. In a recent paper<sup>6</sup> there was stressed the increased frequency of metabolic and nervous breakdown that accompanies such migration, as well as the greater severity and earlier death from arteriosclerosis among these people. The present findings in regard to tuberculosis only emphasize further the hazards of such migration. Tuberculosis among Southerners, both white and black, in their home states along the Gulf is not nearly such a problem as it is among those who have migrated northward. No doubt similar findings would be made for all other forms of respiratory disease if statistics were available.

The findings here presented for tuberculosis, added to those for the degenerative diseases, point out the public and personal health dangers of undirected migration. The time cannot be very far distant when the Federal Government will exercise a close supervision over population movements within, as well as into, the country for both health and economic reasons.

The statistics here presented seem to indicate clearly a marked difference in both whites and blacks in regard to resistance against tuberculous invasion. Energizing climates seem to instill into people an increased ability to fight the infection; but, if such climates are energizing because of wide storm fluctuations, the frequency of infection will be greater. Whether eventual stabilization will take place in stormy areas at a sufficiently high level of resistance to reduce the disease incidence remains to be seen. The constantly declining tuberculosis death rate should not be viewed too hopefully in this respect, since it may largely be due to improved care and personal hygiene of individuals rather than to mass changes in resistance.

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## OBTAINING PERMISSIONS FOR AUTOPSIES.

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THE medical profession of this country recognizes the fact that autopsies are of the greatest importance and that medical knowledge cannot progress in a satisfactory manner without them. But the obtaining of permission from the nearest relatives is often a difficult problem, especially in a small hospital which admits all sorts of cases, both private and charity, and including numerous accident victims. In such a hospital the request must usually be made by the resident staff since they are on duty for the 24 hours of the day, and since they may be the only physicians to come in contact with the family of the patient before death.

At the Millard Fillmore Hospital the interns are prepared for this duty, when they first enter the institution, by impressing upon them the importance of autopsies and explaining how valuable such examinations will be to them; in short, by selling them the idea. Then they are coached in the technique of asking for permission and of convincing the relatives of its importance and the necessity for it. They are required to make the request of the relatives of every patient who dies in the hospital and, following each interview, they must fill out the blanks in a report such as is shown in Table 1, and deliver it to the pathologist within 24 hours. It is natural for a man to perform a duty in a more conscientious manner when he must report it in writing and when it may affect his standing in the hospital and in the eyes of his superiors. This report serves as a check on the energy and effort of the intern; it explains to the pathologist why autopsies were not permitted in some cases; it shows how various factors affect the permissions or refusals of autopsies; and it gives the hospital knowledge of help or interference by its personnel or by outside persons.

When 310 of these consecutive reports had accumulated, they were analyzed for the purpose of getting information which might be of value in obtaining more autopsies. Only adult deaths were considered, for in this hospital the only children are newborn infants who present a very different problem. In this group of 310 deaths there were 180 refusals and 130 permissions, giving an autopsy percentage of 42. But, as shown in Table 2, in 30 of those where no autopsy was performed it was impossible to get in contact with the relatives and so no request could be made. If these 30 were removed from the series, there would be only 280 where a request was actually made and the percentage would then be 46 for the adult deaths.

TABLE 1.—INTERN'S REPORT ON INTERVIEW TO OBTAIN AUTOPSY.

Patient's Name \_\_\_\_\_ Age \_\_\_\_\_  
 Room No. \_\_\_\_\_ Religion \_\_\_\_\_ Nationality \_\_\_\_\_ Case No. \_\_\_\_\_  
 Service: i. e.—Med., Surg., or Obstetrical \_\_\_\_\_  
 Is this a Coroner's Case? \_\_\_\_\_ Attending M.D. \_\_\_\_\_  
 Working Diagnosis: \_\_\_\_\_  
 \_\_\_\_\_  
 Operation: If any \_\_\_\_\_  
 Immediate Cause of Death \_\_\_\_\_  
 Member of Family Interviewed \_\_\_\_\_  
 What Members of the Family were Present? \_\_\_\_\_  
 \_\_\_\_\_  
 Was Autopsy Permission Granted? \_\_\_\_\_  
 To which particular argument do you attribute your success in obtaining the Autopsy? \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 What reasons did the Family give for denying the Autopsy? \_\_\_\_\_  
 \_\_\_\_\_  
 Was this a patient on your regular service? \_\_\_\_\_  
 Did any outside person interfere? \_\_\_\_\_ Who? \_\_\_\_\_  
 Did any outside person help get the Autopsy? \_\_\_\_\_ Who? \_\_\_\_\_  
 Did you get help or interference from the Staff Doctor who attended the Patient? \_\_\_\_\_  
 \_\_\_\_\_  
 Date \_\_\_\_\_ Intern \_\_\_\_\_

NOTE.—A complete report must be made to the Pathologist on each death within 24 hours after the interview.

The reasons for refusal by the relatives in 150 cases are shown in Table 2, and include the several reasons sometimes given by one family. Altogether 94 (63%) refused for sentimental reasons, or a general dislike of the idea. But in 26 someone else interfered when the nearest relative seemed willing to have the examination, and in 9 more the relatives feared the displeasure of absent members of the family. In 21 the family felt satisfied that they knew the cause of death and the disease conditions present. This should warn the attending physician against explaining the disease to the family in too great detail and with too great certainty. He must know how uncertain clinical symptoms sometimes prove to be and what unexpected lesions often appear at the autopsy. In 8 the patients themselves had expressed their disapproval of autopsies. In 4 the request was refused by relatives who had seen or heard about autopsies when they worked in hospitals and undertakers' establishments. In 2 more the family were dissatisfied with former autopsies where the incision was much more extensive than promised to them. This emphasizes the fact that autopsies should always be performed in as dignified and unobjectionable a manner as possible so that the entire personnel of the hospital, including the physicians and nurses, do not develop a great distaste of them. It also points out that if promises are not kept, it will result in less autopsies in the future. The series of 310 deaths included 4 Jews only, and 2 of these used their religion

as a basis for their refusal. One man offered to allow an autopsy if the hospital would waive payment of the bill for his wife's care.

TABLE 2.—REASONS FOR FAILING TO OBTAIN AUTOPSIES IN 180 CASES.

			Per cent.
A. Relatives not interviewed . . . . .	30		16.6
	Per cent.		
Could not be located . . . . .	12	40.0	
Too ill or shocked . . . . .	8	26.6	
Escaped interview . . . . .	7	23.3	
Prevented by physician . . . . .	3	10.0	
B. Reasons for refusal in 150 requests for autopsies.			
No reason given . . . . .	47		30.1
Interference from others . . . . .	26		17.3
	Per cent.		
Family . . . . .	16	10.6	
Staff man . . . . .	5	3.3	
Undertaker . . . . .	2	1.3	
Lawyer . . . . .	1	0.6	
Priest . . . . .	1	0.6	
Feared displeasure of rest of family . . . . .	31		20.6
Patient had disapproved of autopsies . . . . .	8		5.3
Did not care what caused death . . . . .	7		4.6
Patient had suffered enough . . . . .	5		3.3
Knew too much about autopsies . . . . .	4		2.6
	Per cent.		
Worked in hospitals . . . . .	2	1.3	
Worked for undertakers . . . . .	2	1.3	
Would do patient no good . . . . .	4		2.6
Former autopsies unsatisfactory . . . . .	3		2.0
	Per cent.		
Mutilation of body . . . . .	2	1.3	
No help in insurance . . . . .	1	0.6	
Jewish religion . . . . .	2		1.3
Wished cancellation of hospital bill . . . . .	1		0.6

On looking over these refusals, it becomes apparent that the only way to overcome this attitude of sentimental objection seems to be the education of the laity and this can be accomplished only by constant, sustained effort on the part of the medical profession and their associates. Also the young physicians can be trained in the best manner of making the requests and in arguments which may overcome the sentimental distaste. As the number of autopsies increase, they will be accepted more and more as the proper and expected thing to do.

The reasons for allowing autopsies to be done in 130 cases are shown in Table 3. On studying these, it is apparent that in the great majority of them (101 or 78%) the relatives consented because they felt that the examination would be of benefit to them. They really wanted to know just what familial diseases might be there to menace them and they wanted to collect insurance or compensation, or they thought that the case might come into court where an autopsy is often necessary. Therefore it seems best to prepare all arguments with this in mind and to present the question to the family as if it were a great benefit to them, as indeed it is, something

for which they do not have to pay, an expensive examination which may be theirs for saying the word. It should be offered as a privilege to them, not as a favor to the hospital or the physicians. Each request should be prefaced by "Wouldn't you like to know?" and ended by a promise to give the family the findings in either a personal interview or by a letter written in simple non-medical words. It should be pointed out that the examination cannot possibly harm or bother the patient but yet can be of much benefit to the survivors. Also a sympathetic attitude should be maintained during the interview and unpleasant words avoided. The expression "operate after death" usually gives no offense.

TABLE 3.—REASONS FOR 130 PERMISSIONS FOR AUTOPSIES.

	Number.	Per cent.
To obtain accurate knowledge of cause of death . . . . .	60	46.1
Wish to give help in treating others . . . . .	39	30.0
To obtain help in collecting insurance . . . . .	21	16.1
To determine what diseases were in the family . . . . .	18	13.8
Granted without any particular argument . . . . .	14	10.7
To please the attending physician . . . . .	4	3.1
Because of being an unusual case . . . . .	4	3.1
Because patient approved of autopsies . . . . .	2	1.5
To avoid calling the coroner . . . . .	2	1.5

Thirty-nine, however, permitted the examination in the hope that it might be of benefit in improving the treatment for others. So the unselfish argument may work when recital of the benefits to be attained, does not impress the family. Fourteen assented without any particular argument. They seemed to consider that an autopsy should be done as a matter of course, as a natural sequence of death. Such an attitude is the result of education and of consideration of the subject during the years before the emergency of death overtook a member of the family. In 2 cases the patients themselves had expressed a wish to have an autopsy performed. Four consented to please the physicians who seemed to want one. The influence of the attending physician is great and no large number of autopsies can ever be obtained without his coöperation and help. The resident staff should have, at all times, the backing of the attending staff in the form of influence and added arguments. In many instances a few words from the physician even over the telephone, is sufficient to obtain permission. In this series of 130, the attending physician helped, materially, in 53. In 11 more, the autopsy was obtained by other persons persuading the nearest relative to consent. Seven of these were friends and 4 were members of the family by either blood or marriage. The coroner used a favorable influence twice and the undertaker, the special nurse, and a priest each once. In 4 cases, consent was given because an unusual case was recognized and in 2 cases an autopsy was permitted rather than have the coroner called.

In this series of 310 reports of interviews, other factors which might have a bearing upon either consent or refusal were studied in

detail. Sex made very little difference since there were only a very slightly higher percentage of permissions in males. The interns seemed to get just as many permissions on substitute services as on their own. The 130 permissions were divided equally between the ward and private patients, but two-thirds of the refusals were among the private patients and but one-third were in ward cases. So the private patient, with his supposedly greater intelligence and experience, is no more amenable to arguments and reasoning along this line than is the charity patient.

A slightly larger percentage of permissions were obtained in coroner's cases than in others. This can be explained by the possibility of legal action of some kind in a large number of accidental deaths. Slightly fewer permissions were obtained in cases which had been operated upon, probably because the operation usually had revealed the disease conditions present, and the family may feel that the physician had his chance at the operation and there is no need to examine the vital organs again.

There seemed to be very little difference in the percentages of permissions among the different services, with the exception of obstetrics. Here the husband seemed to realize that death had been caused by some sort of an accident and he gave permission in the hope that help might be given to some other woman to whom a similar accident might happen in the future. The nationality made comparatively little difference with the exception of the Jews and the Poles. No autopsies were obtained in the 4 deaths of Jews and the great majority of the Polish patients refused to allow them. The Americans showed slightly more permissions than refusals.

One would naturally think that better results could be obtained by interviewing the nearest relative alone, but such was not the case. Slightly better results were obtained when several members of the family were present, for, although there was some interference, in other cases help was given. Wives permitted a higher percentage of autopsies upon the bodies of their husbands than did husbands upon their wives. This may be explained by the fact that many wives consented in the hope of collecting insurance or compensation while the average husband could expect no monetary benefit. Also the average male is more predatory and would object to the supposed desecration of a body which had been under his care and protection. This is borne out by sons giving more refusals than permissions. Sisters usually refused as did sons-in-law, but the latter felt that they did not have the real right of decision and they feared criticism from friends and other distant members of the family. Daughters, fathers and brothers showed slight differences but mothers gave a few more refusals than permissions.

More refusals were encountered among the Catholics than the Protestants. This may be accounted for by the large number of comparatively ignorant foreign people among the Catholics of this city. Among the 122 Catholics interviewed, two-thirds refused

and only one-third gave permission. Among the 172 Protestants, slightly more than half (53%) refused while 47% consented. A comparison of the age groups showed little of interest until the ages of 70 to 80 when there was 3% of refusals as compared to 14% of permissions indicating that there is less objection to having autopsies performed in older people.

**Summary.** 1. The majority of relatives object to autopsies for sentimental reasons.

2. The majority of relatives who permit autopsies do so because they feel that they, as a family, will benefit from them.

3. All requests should be made of the relatives from the point of view that the family will derive the greatest amount of benefit from the autopsy.

4. Autopsies can only be obtained by constant effort on the part of the medical profession. Physicians must first be convinced of the importance of the examination and then they must use every effort to persuade the relatives to consent to them.

5. The resident staff can be trained in the technique of obtaining autopsies but they must always be able to depend on the attending staff for help and encouragement.

6. Requiring an intern to write a report of every interview will have a good effect upon him and will bring out many interesting facts concerning the obtaining of autopsies.

7. Physicians should not explain the cause of death with too much certainty to the family, as it may prevent autopsies.

8. The pathologist should confine his examination to the limits promised to the family and he should make the examination as little objectionable as possible to the spectators.

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## THE EFFECT OF STANDARDIZED EXERCISE ON THE FOUR-LEAD ELECTROCARDIOGRAM.

### ITS VALUE IN THE STUDY OF CORONARY DISEASE.\*

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THE difficulty of evaluating the condition of the coronary circulation from clinical data alone has been one of the reasons that

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efforts have been directed to utilize the electrocardiogram as a supplement. Recent studies of the 4-lead electrocardiogram have shown the merit of this approach<sup>1</sup>; the present report deals with the possibility of using an exercise test as a further adjunct in such examinations.

It has been shown that changes in the electrocardiogram similar to those described in spontaneous attacks of angina pectoris<sup>2-8</sup> can be elicited in an attack induced by exercise.<sup>5,7,8,9</sup> These observers found, however, that the electrocardiographic changes were not always present when the anginal attack appeared, that they sometimes occurred when the anginal symptoms were absent, that no quantitative relationship existed between the electrocardiographic changes and the anginal attack, and that the electrocardiographic changes did not coincide in time with the anginal attack.

It seemed to us that perhaps a better correlation might be obtained if the exercise were standardized and if 4 leads instead of 3 were employed, particularly since recent work<sup>1,10-14</sup> has shown that Lead IV (or Lead V) enhances the value of the electrocardiogram in coronary disease.

After preliminary trials, we decided to use an exercise which the patient could perform while lying in bed. The exercise consisted of raising a 3-pound dumbbell in each hand by extending the arms fully at right angles to the trunk a total of 60 times in 3 minutes. A 4-lead control record was taken in each instance before the exercise, another set was taken immediately after the exercise and a third set about 7 minutes later. Lead V was found to be more suitable than Lead IV for this test and was used throughout. This exercise test was carried out in 20 patients from the Adult Cardiac Clinic having a history of angina pectoris on effort. The effect of the test on the 4-lead electrocardiogram and on the development of angina was correlated with the appearance of the electrocardiogram at rest.

The results are shown in Table 1. It was found that this exercise led to an angina attack in 13 of these patients. The other 7, while complaining of fatigue in the arms from the effort, did not develop any anginal symptoms. The anginal attacks which occurred were mild, resembling the onset of spontaneous attacks. This is no doubt due to the fact that the amount of effort is limited by the development of fatigue in the arms.

The effect of the exercise on the electrocardiogram of patients as far as the standard 3 leads are concerned is in accord with previous work. We found that there is no parallelism between the development of anginal pain and electrocardiographic changes, sometimes one or the other is absent, sometimes both are absent, sometimes both are present. The addition of the fourth lead was found to be of value in at least 2 patients where the changes following exercise were limited to this lead alone (Table 2). In many of the other



TABLE 1.—SYNOPSIS OF RESULTS.

Patient.	Appearance of control electrocardiogram.		Changes in electrocardiogram after exercise.	
	Leads I, II and III.	Lead IV (V).	Leads I, II, III.	Lead IV(V).

*Angina Did Not Develop After Exercise.*

1	Normal; left axis shift	Normal	None	None.
2	Normal; left axis shift, $T_2$ —	Normal	None	None.
3	Abnormal; L.V.P., Q-R-S slurred, low "voltage"	Normal	None	None.
4	Abnormal; left axis shift, Q-R-S slurred, $Q_2$ present	Normal	None	T smaller; S-T+.
5	Normal; $T_2$ —, left axis shift	Normal	S- $T_{1,2}$ —, $T_2$ smaller	T smaller, S-T+.
6	Abnormal; L.V.P., Q-R-S slurred, T small and —, S- $T_1$ —, S- $T_2$ +	Abnormal; Q-R-S small	T more + or became +, S- $T_1$ more —, S- $T_2$ —, S- $T_3$ isoelectric	T deeper.
7	Abnormal; Q-R-S slurred, T—, S- $T_1$ —, S- $T_2$ +	Abnormal; Q-R-S mainly up, S-T—	Q-R-S $_1$ smaller, Q-R-S $_2$ taller, S- $T_1$ more —, S- $T_2$ more +	S-T less —, T deeper.

*Angina Did Develop After Exercise.*

8	Normal	Normal	None	
9	Abnormal; $Q_2$ present, $T_2$ —, Q-R-S slurred	Normal	S- $T_2$ —	None.
10	Abnormal; L.V.P., $T_1$ —, S- $T_1$ —, S- $T_2$ +, Q-R-S slurred	Abnormal; Q-R-S 1st phase up, S-T—	None	None.
11	Abnormal; Q-R-S slurred, L.V.P., low "voltage"	Normal	None	None.
12	Abnormal; L.V.P., Q-R-S slurred, $T_2$ inverted	Abnormal; Q-R-S up	None	None.
13	Abnormal; L.V.P., Q-R-S slurred	Abnormal; Q-R-S inverted	S- $T_2$ —, $T_2$ smaller	None.
14	Abnormal; L.V.P., Q-R-S slurred, S- $T_{1,2}$ —, S- $T_3$ +	Abnormal; Q-R-S mainly up, S-T negative	S- $T_{1,2}$ more —, S- $T_3$ less +	T very deep.
15	Abnormal; L.V.P., Q-R-S slurred, low "voltage," S- $T_3$ +	Abnormal; Q-R-S up and small, T small	S- $T_{1,2}$ —	T deeper.
16	Abnormal; Q-R-S diphasic and slurred	Abnormal; Q-R-S small, T+	None	T less +.
17	Abnormal; Q-R-S slurred, left axis shift, $T_2$ —	Normal	$T_1$ taller, $T_2$ deeper, S- $T_{1,2}$ —	T deeper.
18	Abnormal; L.V.P., Q-R-S slurred, T small, $T_{2,3}$ —, S- $T_1$ —, S- $T_2$ +	Normal	$T_2$ +, $T_1$ more +, S- $T_1$ more —, S- $T_2$ more +	T deeper, S-T+.
19	Abnormal; L.V.P., Q-R-S slurred, S- $T_{1,2}$ —, S- $T_3$ +	Abnormal; Q-R-S up	$T_2$ —, S- $T_2$ isoelectric, S- $T_{1,2}$ more —	T deeper.
20	Abnormal; Q-R-S $_1$ small and diphasic, S- $T_{2,3}$ —, Q-R-S slurred	Normal	T smaller, Q-R-S $_1$ inverted, S- $T_{2,3}$ more inverted	T smaller, S-T+.

L.V.P. = Left Ventricular Preponderance; — = negative; + = positive.

records the magnitude of the change in the fourth lead was of great value in confirming the impression that the exercise had caused electrocardiographic alterations. Nevertheless it must be pointed out that even when the 4 leads were used, exercise on occasion had no demonstrable action on the electrocardiogram. The deductions obtained from 3 leads still hold when 4 leads are used but the number of negative responses is reduced (Tables 2 and 3).

TABLE 2.—SUMMARY SHOWING LEADS OF ELECTROCARDIOGRAMS IN WHICH CHANGES OCCURRED.

	Electrocardiogram changed after exercise in:				Electrocardiogram in control.			
	All 4 leads.	Only Leads I, II, III.	Only Lead IV (V).	None.	Abnormal in			Normal in all leads.
					All leads.	Only Leads I, II, III.	Only Lead IV (V).	
Patients developed angina after exercise	6	2	1	4	7	5	0	1
Patients not having angina after exercise	3	0	1	3	2	2	0	3
All patients tested	9	2	2	7	9	7	0	4

The changes in the ordinary 3 leads following exercise (Table 1 and Fig. 1) were: (1) An axis shift to the right in a few instances; (2) a change in the *T* wave in a direction opposite to the major *Q-R-S* deflections; and (3) most striking, a tendency of the *S-T* segment to shift in a downward direction, viz., a positive *S-T* segment became less positive, isoelectric or even negative, an isoelectric *S-T* segment became negative and a negative *S-T* segment became more negative. However, in 1 or 2 instances the *S-T* segment in Lead III shifted in the opposite direction when the *Q-R-S* was down and deep in this lead.

The changes in Lead IV (or V) (Table 1 and Fig. 1) were characteristic when they occurred. They consisted of a shift in the *S-T* segment upward so that at times the *S-T* segment became positive. The *T* wave usually became deeper (or a positive *T* wave less positive); however, in a few instances the *T* wave became smaller. In all instances where a change occurred, the most significant alteration was a positive angular movement of the *S-T* segment, making the angle between the *S-T* segment and the descending limb of the *T* wave more acute. This is clearly to be seen in Fig. 1.

The majority of the patients had abnormal electrocardiograms of varying degrees (Tables 1 and 2). Only 4 had 4-lead electrocardiograms within normal limits. Lead IV was never found to

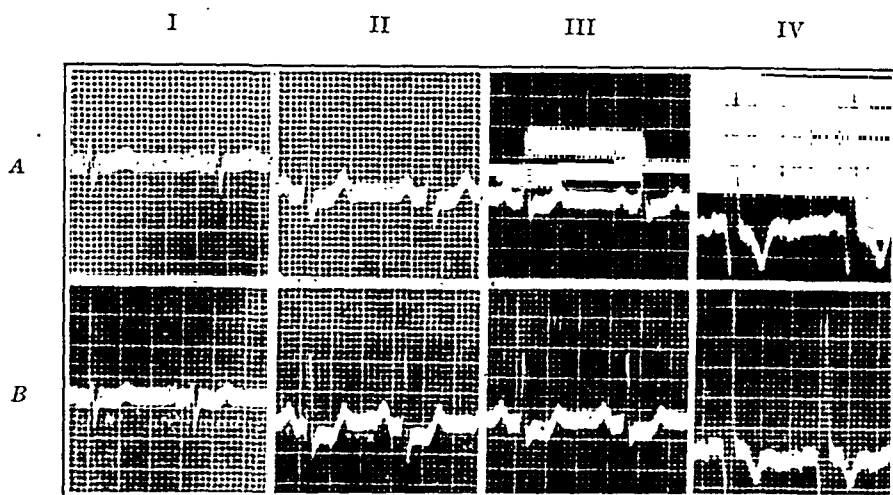


FIG. 1.—Segments of four-lead electrocardiogram, showing effect of exercise test on records in Patient 20. A is control before exercise; B, after 3-minute exercise.

TABLE 3.—SUMMARY CORRELATING (1) OCCURRENCE OF ANGINA AFTER EXERCISE, (2) APPEARANCE OF THE CONTROL ELECTROCARDIOGRAM AND (3) OCCURRENCE OF CHANGES IN THE ELECTROCARDIOGRAM AFTER EXERCISE.

	Patients developing angina after exercise.		Patients not having angina after exercise.		All patients tested.	
	4-lead electrocardiogram.		4-lead electrocardiogram.		4-lead electrocardiogram.	
	Normal.	Abnormal.	Normal.	Abnormal.	Normal.	Abnormal.
4-lead electrocardiogram shows changes after exercise . . . . .	0	9	1	3	1	12
4-lead electrocardiogram does not show changes after exercise . . . .	1	3	2	1	3	4

be abnormal when the other 3 leads were normal, but the reverse was true in many patients (Table 2). The appearance of the 4-lead electrocardiogram in patients with coronary disease is discussed in more detail in another communication where a larger series were studied.<sup>1</sup>

An analysis of the correlated data as assembled in Tables 2 and 3 leads to the following tentative conclusions:

The appearance of the 4-lead electrocardiogram taken at rest, the effect of a standardized exercise on the 4-lead electrocardiogram and the effect of such an exercise in producing anginal attacks are to be regarded as a triad which together augment the knowledge of the condition of the coronary circulation, obtained from clinical examination alone. The fact that a positive findings by one of these three criteria can occur with negative findings by the other two shows the value of relying on a combination of all three, rather than on any one of them alone. There can be no doubt that the fourth lead is a valuable addition to the other leads in carrying out this analysis. This deduction is to be considered no more than a preliminary approach, since the tests have been used in too few patients to warrant final deductions. This study has, however, pointed to the need of expanding the study to a larger group of patients.

One precaution is essential, as our preliminary tests showed, namely, to stop the exercise when generalized fatigue, dyspnea, cyanosis or anginal pain appeared before the 3 minutes were up.

**Summary.** The use of the effect of exercise on the 4-lead electrocardiogram was found to be a valuable adjunct in estimating the status of the coronary circulation. The routine use of some such simple exercise test may be found to be of value in judging a patient's response to effort.

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## THE EFFECT OF SCARLET FEVER UPON THE HEART.\*

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ALTHOUGH it is often stated that scarlet fever is a potential cause of heart disease, existing clinical descriptions of so-called "scarlatinal endocarditis" are far from agreement. It was in the hope of defining the condition more clearly that this study was undertaken.

The importance of the problem is attested by reports from various quarters of the incidence of endocarditis in scarlet fever.<sup>1,2,3,4</sup> Some of these are briefly summarized in the table. While such statistics are of considerable interest, the diagnosis of acute endocarditis in the presence of infection is fraught with such difficulty as to raise serious question as to their quantitative value. To meet such objections the disease has been studied from two points of view: first, from the electrocardiographic angle during the acute phase, an approach which has the advantage of complete objectivity; and second, from an estimation of the end results in the form of chronic valvular disease following upon scarlet fever.

1. ELECTROCARDIOGRAPHIC AND CLINICAL STUDY DURING COURSE OF DISEASE. It was hoped that the electrocardiograph might afford some new evidence as to the type and perhaps the incidence of the cardiac involvement. The method had been employed by Shookhoff and Taran (1931) in 50 consecutive cases of scarlet fever.<sup>5</sup> They found no prolongation of the *P-R* interval but did observe in Leads I and II minor changes in the position of the *R-T* or *S-T* interval in 14% and "abnormalities in shape and direction of the *T*-wave" in 10%. "All abnormalities occurred early in the course of the disease and disappeared early in convalescence."

A group of 171 scarlet fever patients has been studied electrocardiographically at the South Department of the Boston City Hospital. The cases were observed during the years 1932, 1933 and 1934, a time when scarlet fever was relatively mild in character. There was no selection of cases except in favor of arthritis, all cases

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of scarlatinal arthritis who came under observation during this period being included.

Abnormal electrocardiograms were found in 11 cases, an incidence of 6%. These abnormalities consisted of prolongation of the *P-R* interval beyond 0.20 second in 5 cases and *T*-wave changes in 6 cases. The *T*-wave changes in Lead I or II, or both, consisted of marked temporary diminution in amplitude in 2 cases, flattening in 1 case and inversion in 3 cases. In addition, 8 cases exhibited a *P-R* interval of exactly 0.20 second (a suggestive finding, at least, in the 5 cases who were less than 14 years of age).

*Arthritis.* Included in this group were 29 cases of scarlatinal arthritis. Of these only 2 showed definite electrocardiographic changes and 3 a *P-R* interval of 0.20 second.

*Age.* The ages of all those who developed abnormal records were between 4 and 16 years. Seventy-five per cent of the patients fell within this age period.

*Sex.* Six of the cases showing abnormal electrocardiograms were males and 5 were females.

TABLE 1.

Author.	Source.	Number of cases of scarlet fever.	Number of cases of endocarditis.	Percentage of cases of endocarditis.	Number of cases of pericarditis.	Percentage of cases of pericarditis.
McCollum <sup>1</sup>	Boston City Hospital	3,000	16	0.50	18	0.60
Broadbent <sup>2</sup>	Metropolitan Asylums' Board	22,096	129	0.58	..	0.08
Broadbent <sup>2</sup>	London Fever Hospital	("period of 5 years")	....	1.80	..	0.15
Nobecourt <sup>3</sup>	French Army	278	7	2.50	2	0.70
Joe <sup>4</sup>	Edinburgh City Hospital	24,102	61*	0.25*	61*	0.25*

\* Figures include both endocarditis and pericarditis.

*Severity.* There appeared to be no relationship between the severity of the scarlet fever and the incidence or degree of electrocardiographic abnormalities.

*Time of Onset.* Perhaps the most interesting feature of the study was that no abnormality was found in any electrocardiogram taken before the 13th day of the disease (although 61 records were taken during the first 12 days) (Fig. 1). The majority of the abnormal records were grouped between the 18th and the 34th days. This delayed reaction is comparable to that seen in the cardiac involvement of diphtheria or the recrudescence of rheumatic fever following a respiratory infection. It is in contrast to the immediate electrocardiographic changes sometimes noted in very severe acute infections, such as lobar pneumonia.

*Fever.* The delayed appearance of the electrocardiographic changes was associated with a recrudescence of fever in 5 cases. In 3 cases where the temperature curve was not complicated by secondary infection or possible serum reaction, the time from the onset of the scarlet fever to the onset of the secondary reaction was 16, 24 and 29 days, respectively. Figure 2 illustrates this reaction and its relation to the electrocardiographic changes. In this instance, the secondary reaction was not accompanied by arthritis, the only clue to its real significance being furnished by the electrocardiogram.

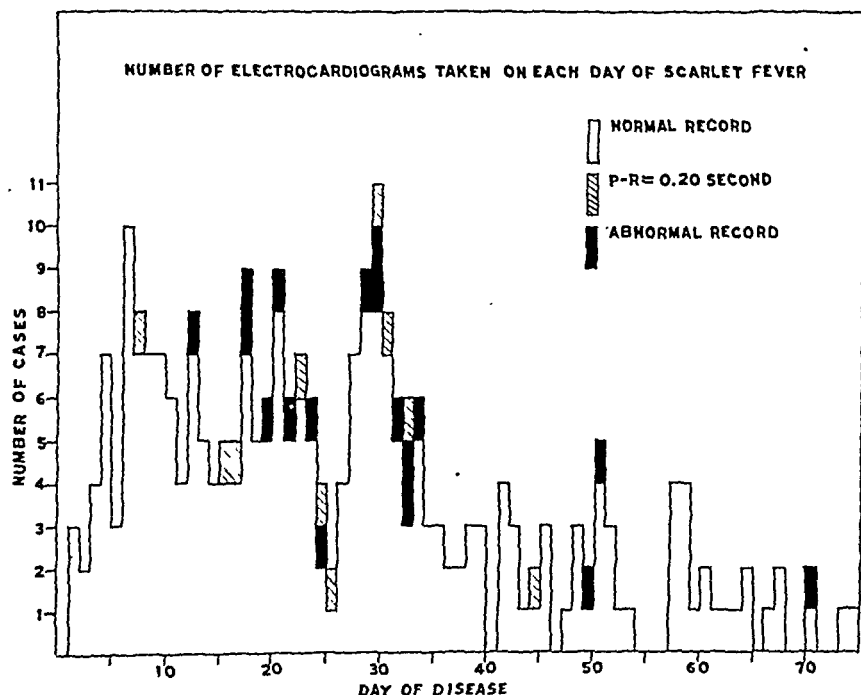


FIG. 1.—Latent period between the subsidence of the acute scarlatinal infection and the appearance of a secondary reaction characterized by fever, tachycardia and prolongation of the P-R interval without, in this instance, any arthritis.

Particular emphasis has been laid on the electrocardiographic findings on account of their objectivity but the clinical evidence of cardiac involvement is nevertheless of some interest.

There were 6 cases of old rheumatic heart disease. Of these 5 showed no clinical or electrocardiographic signs of reactivation. The 6th case developed both clinical and electrocardiographic signs of reactivation with a complicating pericarditis.

There were 4 cases which developed clinical signs of endocarditis immediately following the scarlet fever. Of these cases 3 exhibited both systolic and diastolic murmurs at the apex, the 4th developed a very harsh systolic murmur at the apex. One of them showed

enlargement of the transverse diameter of the heart by Roentgen ray measurement (cardio-thoracic ratio 59%). Another showed a distinct "mitral bulge" in the upper left border of the Roentgen ray silhouette of the heart. Of the 4, 2 had electrocardiographic evidence of involvement and 2 had none.

Five cases who showed positive electrocardiograms had no clinical signs of cardiac involvement and 3 others showed only systolic murmurs.

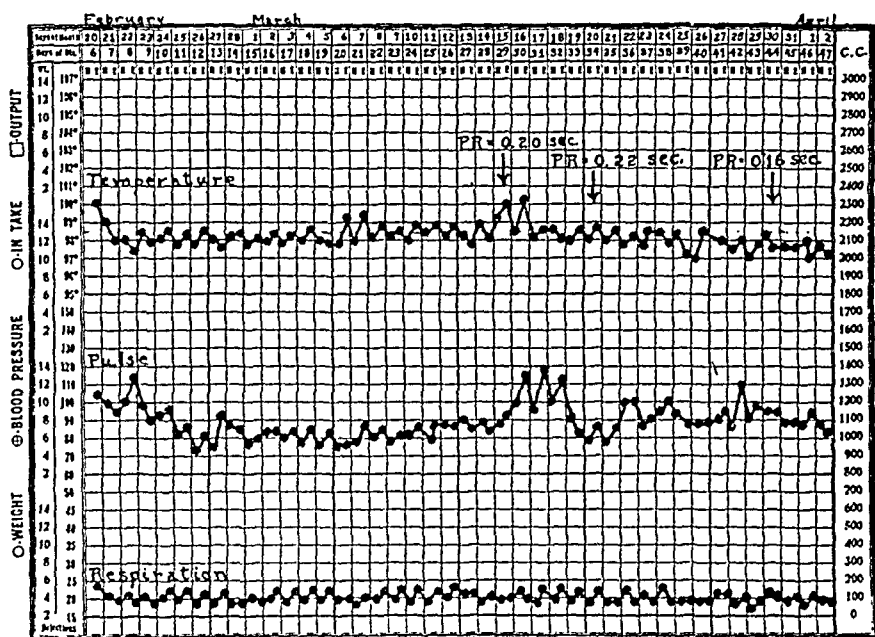


FIG. 2.—Delay in appearance of electrocardiographic abnormalities following scarlet fever. The tendency for these abnormalities to disappear is also suggested. Of 61 records taken between the 2d and 12th day of the disease, inclusive, none was abnormal. Of 138 records taken between the 13th and 33d days, inclusive, 15 were abnormal. Of 70 records taken between the 34th and 75th days, inclusive, only 3 were abnormal.

Seventeen patients, who showed no electrocardiographic abnormalities, developed systolic murmurs of differing grades of intensity, most of them apical, but without other signs of valvular disease.

2. FOLLOW-UP STUDY. Another approach to the problem of the rôle of scarlet fever in the production of heart disease is through a follow-up study of a large number of cases. This was done on a very small scale in Nobecourt's thorough investigation outlined in the table. He found that only 2 of the 7 soldiers who had "acute scarlatinal endocarditis" developed chronic endocarditis.

The present report is based on a follow-up examination of 600 cases from 1 to 3 years after scarlet fever. The examinations were carried out in the years 1931 and 1932 on individuals who had previously been treated at the South Department of the Boston



City Hospital for scarlet fever. These people returned to the hospital for examination in response to letters requesting them to do so. No selection of cases was made and the group appeared to be a representative cross-section of the patients who had passed through the scarlet fever wards during the period.

All persons in whom there was either a doubtful or positive diagnosis of cardiac disease were examined by at least two of the authors and received electrocardiograms and Roentgen ray measurements of the heart. The results of the follow-up study were compared with the original hospital record in each instance.

Of the 600 cases, only 7 had developed signs of chronic valvular disease during the interval. In 2 cases the signs of endocarditis had developed in the hospital before discharge from quarantine. In a third a typical attack of rheumatic fever had followed immediately after his discharge from the ward. Another had suffered from 3 attacks of rheumatic fever during the interval between the scarlet fever and the follow-up examination. In the remaining 3 cases, the physical signs of valvular disease were found without any intercedent history of rheumatic fever or chorea.

Of these individuals, 6 were girls and 1 a boy. Their ages were from 3 to 11 years, with an average of 5.6 years. Three of the cases had been classified as mild scarlet fever, 3 as moderately severe, and 1 as severe. With 1 exception (a case complicated by mastoiditis and operation) the patients were in the hospital the usual length of time (from 28 to 47 days). Except for the case of mastoiditis just mentioned there were no other important complications in the group who developed heart disease. There was no arthritis or nephritis in this group. Only 1 case exhibited a rise in temperature after the initial pyrexia had subsided and this was 1 of the 2 cases in which the diagnosis of acute endocarditis was made.

The type of heart lesion was indistinguishable clinically from "rheumatic" heart disease. Four of the patients had the characteristic auscultatory signs of mitral stenosis and regurgitation. Another had these signs and also those of aortic regurgitation; 1 had signs of aortic regurgitation alone and 1 of mitral regurgitation alone. It may be pointed out that the occurrence of heart disease in the group under consideration was far greater than would be expected in an unselected group of Boston school children of the same age and social status observed for a like period.<sup>6</sup>

All but one showed Roentgen ray evidence of heart disease. The only electrocardiographic abnormalities found on the follow-up examination were right axis deviation in 2 cases, the slurring of the *Q-R-S* complexes in all leads with a *Q-S* interval of 0.10 second in 1 case.

Hector<sup>7</sup> found that "The almost invariable result of scarlet fever upon the heart already damaged by rheumatism is a rekindling of the old trouble which in some cases had been quiescent for a

considerable period." This has not been our experience. In the follow-up series 4 instances were encountered in which rheumatic heart disease preceded the attack of scarlet fever. In 1 of these a recrudescence of rheumatic fever appeared immediately after discharge from the hospital. In none of this small group, however, did the follow-up examination indicate that the cardiac status had been significantly altered by the scarlet fever.

**Discussion.** All the findings in the acute and late phases of cardiac involvement in scarlet fever are analogous to the changes seen in rheumatic fever following acute tonsillitis. The importance of hemolytic streptococcus infections of the upper respiratory tract in precipitating rheumatic fever is well recognized. In both conditions there is often a well defined latent period of several weeks between the respiratory infection and the secondary constitutional reaction. In both, similar electrocardiographic signs of cardiac involvement may appear following a latent period. In both, endocarditis may occur with or without an acute migratory arthritis.

The arthritic manifestations in scarlatinal and rheumatic arthritis are so similar that in individual cases the differential diagnosis would be impossible without the history. However, if a large group of cases of scarlatinal arthritis is studied, certain differences from typical rheumatic fever stand out. These differences consist of a relatively greater incidence of involvement of the small joints in the case of scarlet fever, with a generally milder course and less effusion into the joints.<sup>4</sup> Also our figures, showing abnormal electrocardiograms in only 2 cases out of 29 of scarlatinal arthritis, are not as high as one would expect in rheumatic fever. On the other hand, there are plausible explanations for these discrepancies. The comparative youth of the scarlatinal patient would tend to mitigate the severity of the arthritis if it is of the type associated with rheumatic fever. (The average age of the 600 scarlet fever patients in the follow-up study was only 6.3 years.) It has been our experience, too, that electrocardiographic changes are less common in the younger patient with rheumatic fever. The striking similarity of the two conditions is obvious; the question of whether their differences are fundamental is doubtful.

Of the valvular involvement resulting from scarlatinal endocarditis one can only say that it is indistinguishable clinically from rheumatic endocarditis. The same may be said for the pericarditis associated with both conditions. The fact that scarlet fever caused a reactivation of infection in patients with rheumatic heart disease in only a minority of cases is only in keeping with the effects of other streptococcus infections of the respiratory tract in such cases. In hospitalized cases of rheumatic infection, streptococcus respiratory infections were followed by recrudescence of rheumatic manifestations in only 50%. One would expect the incidence to be less in cases of presumably inactive rheumatic heart disease.

Finally, it has been our privilege to observe in a recent case of post-scarlatinal endocarditis the appearance of typical rheumatic subcutaneous fibroid nodules.

The similarity and possibility of relationship between rheumatic and scarlatinal heart disease has been commented upon by others.<sup>7,8,9,10</sup> The evidence is now complete enough to indicate that they are probably identical. Interpreted in the light of Swift's allergic hypothesis, this means that a properly sensitized individual may respond to an infection with *Streptococcus scarlatinae* by the allergic reaction known as rheumatic fever. There is no evidence that this reaction differs significantly from rheumatic fever following other streptococcus infections of the upper respiratory tract. Such a concept explains, in part, the absence of Aschoff bodies and other characteristic features of rheumatic fever in routine postmortem studies of scarlet fever.<sup>11</sup> The altered tissue reaction which characterizes rheumatic fever would only rarely be met with under such circumstances.

**Summary.** An electrocardiographic study was made of 171 cases of scarlet fever during and following the acute infection. Abnormal electrocardiograms were noted in 11 cases. The abnormalities consisted of prolongation of the *P-R* interval in 5 cases and flattening or inversion of the *T* wave in 6 cases and did not appear before the 13th day from the onset of the scarlet fever in a single instance.

A follow-up study of 600 cases of scarlet fever was made from 1 to 3 years after the acute infection. It was found that 7 of these individuals had developed heart disease in the interval. The type of heart disease found was indistinguishable clinically from rheumatic heart disease.

Since this paper was written a valuable contribution to the problem has been published by Paul and his coworkers which in general supports our conclusions. (Paul, J. R., Salinger, R., and Zuger, B. Relation of Rheumatic Fever to Post-scarlatinal Arthritis and Postscarlatinal Heart Disease—Familial Study. *J. Clin. Invest.*, 13, 503, 1934.

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## THE MIGRAINE PHYSIQUE.

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THE riddle of migraine has developed a truly enormous literature<sup>1</sup> dealing with the many aspects of the problem. The functional nature of the attack,<sup>2</sup> the relation of the migraine seizure to epilepsy,<sup>2</sup> the etiologic significance of heredity,<sup>3,4</sup> allergy,<sup>5-9</sup> gonadal function, ocular defects<sup>10,11</sup> and fatigue,<sup>12</sup> and the prophylactic and active therapy<sup>2</sup> all have been repeatedly and voluminously discussed. However, it has not been possible to find any discussion of a characteristic physique in relation to migraine. Our own observations have strongly indicated that there is such a characteristic physique, or constitutional type, in which migraine appears with extraordinary frequency. It has been commonly possible to predict migraine in persons after but a cursory inspection and analysis of certain typical features.

Migraine long has been known to be familial and much has been written emphasizing the hereditary nature of the disturbance. Allergic tendencies are likewise recognized as being hereditarily transmissible, and the relationship of allergy to migraine seizures recently has received much emphasis. It is thus not surprising that along with these two significant observations there should be a characteristic constitutional type in which migraine, in one or more of its many forms, occurs with unusual frequency. Naturally, not all migrainous individuals conform to this characteristic type any more than all instances of cholecystitis appear in short, stout individuals, or pulmonary tuberculosis in those of the Stillar physique, but the incidence is amply high to justify correlation.

The stimulating work of Draper<sup>13</sup> and others<sup>14,15</sup> reminds us of the importance of fundamental constitutional characteristics in the causation of disease. Recognition of well-defined constitutional types does not aid appreciably in direct therapy, but should aid in creating a somewhat clearer understanding of the disease.

The frequency of the various characteristics of the migraine physique have been noted and tabulated in an unselected consecutive series of 100 cases of migraine seen in private practice. These data emphasize the frequency with which certain features are notable. The outstanding characteristics of the physique may be described briefly as follows:

1. Neither height nor weight are unusual, although extremes of variation are perhaps more frequent than in normal persons.

2. The hair is almost invariably characteristic—very fine and slender, straight and typically brunette. Migraine is most unusual in true blondes. The hair is neither unduly scant nor heavy, but is frequently rather more oily than usual. The significant feature is the soft, fine texture; it is never stiff and rarely naturally curly.

3. The eyes reveal unusually large pupils in proportion to the exposure to light. It has been noted repeatedly that this pupillary dilatation is exaggerated still further with fatigue and is especially marked just prior to an attack of migraine. Habitual pupillary dilatation occurred in 96% of the patients tabulated, and in the remaining 4% there was 1 instance of Argyll-Robertson pupils due to syphilis. These dilated pupils, however, react normally to light and accommodation, although they do not contract as firmly as the normal.

4. The skin is typically thin and fine and unusually smooth—more like a child's skin than that of an adult. It gives the impression of unusual transparency. Pallor is more common than ruddy facies. The facies are most commonly characterized by finely chiseled classical features with delicate moulding, narrow nostrils and small nasal alæ.

5. The extremities are habitually cold and frequently moist and clammy. Such cold and moist extremities were noted in 91% of these patients.

Other less obvious characteristics of these patients are an unusual lability of the arterial tension and pulse rate.<sup>16</sup> (See Table 1.) Of the instances of hypertension, 7 cases were of the emotional type, described previously.<sup>17</sup> The notable frequent coincidence of arterial hypotension is significant.<sup>18</sup> A history of attacks of typical paroxysmal tachycardia<sup>2,19</sup> was obtained in 49% of these patients.

The usual pallor of the skin may or may not be associated with the high incidence of secondary anemia. Apokamnosis and habitual fatigue are characteristic, occurring in 82% of the patients.<sup>12</sup> It is probable that there exists a distinct relation between the tendency to arterial hypotension and anemia and this marked diminution of endurance. The typical migraine patient fatigues readily and is, in fact, habitually tired. Almost all of the female patients (91% women) complained of marked exaggeration of this sense of fatigue or exhaustion just prior to their menstrual periods. Upper respiratory tract infections and chronic infections were conspicuously unusual, although rheumatic infection was surprisingly frequent. Some form of rheumatic carditis and chilling or chorea occurred in 15% of these patients, whereas all other infections totaled but 17%.

A tabulated summary of these 100 cases of migraine will illustrate the significant characteristic features.

TABLE 1.—CHARACTERISTIC FINDINGS IN 100 CASES OF MIGRAINE.

1. SEX.\* Male, 14%; female, 86%.
2. AGE. Average, 31.4 years (extremes, 58 to 18).
3. CIRCULATORY OBSERVATIONS. Arterial tension: Average, 124.6/78.4 (extremes, 210/125 and 90/60); normal tension, 41% (increased 19%; decreased 38%). Pulse rate: Average, 85 (over 90, 21%; 70-80, 73%). History of paroxysmal tachycardia, 49%. Cold, moist extremities, 91%. Hemoglobin: Average, 72.3% (Dare); above 80%, 18%; 70-80%, 26%; 60-70%, 31%; undetermined, 25%.
4. NEUROLOGIC OBSERVATIONS. Pupils large, 96%; normal, 3%; Argyll-Robertson, 1%; History of scotomata, 54%. History of vertigo, 72%.
5. HAIR. Brunette, 93%; blonde, 7%; typically fine and straight, 96%.
6. MARKED APOKAMNOSIS, 82%.
7. POSITIVE FAMILIAL HISTORY, 89%.
8. WEIGHT. Normal, 38%; obese, 25%; underweight, 37%.
9. MENSES. Normal, 6%; marked intoxication, 91%; dysmenorrhea, 63%.
10. COINCIDENTAL DISEASES (frequency of occurrence). Neurologic: Neuritis, 5; psychosis, 3; chorea, 3; petit mal epilepsy, 1. Circulatory: Vasomotor instability, 33; emotional hypertension, 7; arterial hypertension, 19; arterial hypotension, 38; myocardial failure, 5; rheumatic mitral disease, 7; syphilitic aortic disease, 1; secondary anemia, 57. Constitutional: Dystrophia dystocia syndrome,<sup>21</sup> 8; Milroy's disease, 1; thyrotoxicosis, 6; myxedema, 1. Urinary: Calculi, 3; nephritis, 6; cystitis, 2. Gastro-intestinal: Irritable spastic colon, 9; peptic ulcer, 2. Infections: Rheumatic infection, 15; tuberculosis, 4; all other infections, 17.

**Comment.**—The above data demonstrate that the migraine physique is characteristic and should be recognized readily and early. The significant characteristics of the hair, eyes, skin, facies and extremities occur with notable frequency in migrainous individuals. It is an extremely common occurrence that patients with migraine do not volunteer information concerning their attacks. They have had these attacks for years, their mothers before them were similarly afflicted, and they have come to feel that nothing can be done. Because of the continuous apokamnosis or sense of exhaustion and fatigue, ambition becomes dulled and not infrequently a profound belief in constitutional inferiority is of the greatest importance. The intellectual level, however, usually is very high.

Aside from the obvious visible and anatomic findings, some of the physiologic characteristics and consequences deserve comment. Perhaps most significant of these is an undue vasomotor instability.<sup>22</sup> The frequent hypotension, the disturbed peripheral circulation as manifested by pallor and cold, moist extremities, and the high inci-

\* Allen<sup>20</sup> reports that the ratio of men to women suffering from migraine is about 1 to 21; Draper<sup>13</sup> reports 1 to 7.

dence of paroxysmal tachycardia illustrate some ill-defined but quite obvious constitutional defect in the equilibratory mechanism of the circulatory system. Local circulatory phenomena are often exaggerated. These patients blush readily and excessively, emotional hypertension is not uncommon<sup>17</sup> and vasomotor coryza is frequent. Along with the instability of the circulatory tonus is an emotional instability which is most frequently manifest as depression. If the theory that the acute migraine attack is due to some form of cerebral arteriolar spasm is a correct conception, such constitutional vasomotor instability as herein described would most certainly be a predisposing factor.

Of the greatest importance in understanding the problems of migraine is an appreciation of the significance of habitual fatigue. This apokamnosis is a very real and major problem to the patient, although there may be but negligible objective evidence thereof. Amelioration of this subjective state can do more to improve the morale and happiness of the patient with severe migraine than anything else. The continuous persistence of this subjective languor is destructive to ambition. Habitual anemia, hypotension,<sup>18</sup> the fatiguing effects of glare<sup>19</sup> on the poorly protected retinae and many other factors contribute to the maintenance of this state. Furthermore, we may postulate that these individuals are constitutionally decidedly less resistant to the effects of fatigue than normal persons.

Fatigue may be of various types and origin—physical fatigue, as exemplified by the effects of muscular work; mental or emotional fatigue from excessive or prolonged activity (viz., worry),<sup>23</sup> and also the ill-defined fatigue which follows infectious processes or intoxications. This latter is a more generalized disturbance. It is perhaps most characteristically illustrated by the well-known post-influenzal asthenia. This state of body depletion, exhaustion and vasomotor instability which persists after an influenzal infection closely resembles the habitual state of many migraine patients. One patient defined the condition as “that limp, wet dish-rag feeling.” In postinfluenzal asthenia, as in the migraine constitution, the arterial tension is low,<sup>18</sup> the pulse is rapid, there is frequently undue perspiration, especially of the cold extremities, the patient feels weak and exhausted, and mental as well as physical effort is avoided. The situation is not merely a neurocirculatory asthenia,<sup>12</sup> in which the disturbances become manifest only under condition of stress, but resembles a profound generalized change, such as occurs early in convalescence from an infectious disease or a state of habitual intoxication from some noxa as yet unknown.

The relatively high resistance to acute infections in these patients is of great interest. Acute upper respiratory tract infections are very rare, and with the exception of rheumatic infections, other infectious diseases are unusual. The relationship, if any, of the

relatively frequent finding of rheumatic infection or its effects, with the circulatory instability, warrants further study.<sup>16</sup> Along with this relative immunity to transient acute infections, there occurs a notable thermostability. Patients of the typical migraine physique rarely reveal fever during their infections. If fever does appear, it is of lesser magnitude than one would anticipate from the other evidences of infection. It is important that this fact be given consideration in evaluating the significance of the temperature curve in such problems as suspected or early tuberculosis, pyuria, bronchitis, and the like. The absence of fever, or the appearance of but a negligible degree thereof, may be misleading unless one appreciates this unusual thermostability. As yet, we have no clue whatever to the mechanism of these two phenomena—the relative freedom from acute infections, and distinctly more marked thermostability. There is also no evidence indicating whether or not these two characteristics bear any fundamental relationship to one another.

**Conclusions.** Migraine, long known to be hereditary and, at least in part, of constitutional origin, is very frequently found in persons revealing a characteristic physique or habitat. The more significant structural characteristics are as follows: (1) Very fine, delicate, straight hair, usually brunette; (2) a fine, transparent, childlike skin; (3) unduly large pupils which react normally to light and accommodation; (4) classical, finely moulded features, with narrow nostrils; (5) cold, moist extremities.

This complex, once seen, is readily recognized and is found associated with migraine with great frequency.

The physiologic characteristics are: (1) An unusual degree of vasomotor instability; (2) a markedly lowered resistance to fatigue and, therefore, an habitual apokamnosis; (3) a distinctly increased thermostability; (4) relative freedom from acute infections.

These various characteristics appear with such regularity in patients with migraine that one may justifiably regard them as composing a constitutional type. For this type, for want of a better term, we suggest the term "migraine physique." Recognition of this type does much to clarify some of the problems of migraine. The riddle of migraine is far from being solved, but it is hoped that further study of these interesting constitutional characteristics may be a forward step.

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## RINGWORM OF THE SCALP.

### CURABILITY, WITHOUT DEPILATING MEASURES, OF INFECTIONS CAUSED BY "ANIMAL" MICROSPORONS.

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ROENTGEN RAY therapy, in epilating dosage, is still frequently used in the treatment of tinea capitis in the Eastern United States. In a number of New York institutions it is carried out as a routine procedure. Epilation by means of the thallium salts is not as popular as the former remedy due largely to the toxic results sometimes produced. Both measures require careful preparation of the patient, elimination of unsuitable patients and meticulous attention to the details of the procedure. Both measures also involve a certain amount of risk to the patient, and accidents, while uncommon, are not unknown. In other sections of the country, epilation by means of Roentgen rays or the thallium salts is also frequently practised, but apparently they are not used to a wide extent in the Southern and Western United States where the local application of medicaments is often sufficient to effect a cure. Mook<sup>1</sup> stated that in St. Louis, ringworm of the scalp invariably responded within 3 to 6 weeks to the local application of such remedies as tincture of iodine,

5% ammoniated mercury ointment, or a salve containing 4% salicylic acid and 8% precipitated sulphur. In 29 years, he had only encountered 2 cases (in brothers) where it was necessary to employ Roentgen epilation.

The advantage of curing the disease through the use of topical remedies rather than Roentgen rays or thallium is probably acknowledged by all, but the numerous remedies advocated (which may be found in any standard text on Dermatology), attest to the relative lack of specificity and uncertainty of cure. The search for a specific cure for tinea capitis has been pursued for many years. MacKenna<sup>2</sup> commented that "from time to time some new form of treatment or some modification of an old one is acclaimed as rapid, efficacious and certain. Long experience and the trial of some of these vaunted quick cures has driven me to the painful conclusion that their enthusiastic sponsors are usually youthful optimists who examine their patients with the eye of faith rather than the lens of the microscope." Ormsby stated that "the indication for the relief of trichophytosis capitis is the destruction of the parasite, and there can be no question that this can be accomplished in some cases without having recourse to epilation." This latter opinion appears to be generally held although the indications for the use of depilating measures or the institution of local therapy is not well defined in any of numerous texts consulted. Of the more recent remedies brought forward, certain volatile oils, first shown to have active antifungicidal properties by Myers,<sup>4</sup> and Kingery and Adkinson,<sup>5</sup> were favorably reported upon in a clinical study by Kingery.<sup>6</sup> Loomis,<sup>7</sup> however, was unable to duplicate his results in a series of patients in Cleveland.

The tendency to biologic cure in certain cases of tinea capitis was emphasized in a recent communication.<sup>8</sup> In such cases, "animal" fungi appear to be the usual causal organisms. The fact that in general, cases due to "animal" organisms are easier to cure than the ones in the *M. audouini* group, has been mentioned,<sup>9</sup> but has apparently escaped attention in this country or has not been widely accepted. In order to ascertain the effect, if any, the type of fungus present had on the curability of tinea capitis by the use of topical remedies, a series of patients was treated during the past year. The results are given below.

Forty-nine patients with tinea capitis (including favus) were studied, representing the casual applicant to the dispensary in the service of Dr. Fred Wise and cases from other institutions, and in the private practices of coöperating colleagues, among whom should be mentioned Drs. Van Alstyne H. Cornell, E. A. Abbey, G. Astrachan, and P. S. Kerr. The types of fungi grown, and the incidence follow: *M. audouini* 22; *M. lanosum* 17; *A. schoenleinii* 3; *Tr. violaceum* 1; *M. felineum* 1; no growth 4; undiagnosed 1. Of this number, 37 cases form the basis of this report. The remain-

der (12 cases) either did not continue under observation, or their exact status was undetermined. Laxity in carrying out the treatment was not deemed sufficient reason for excluding several cases since this was not confined to any one group. The 37 cases herewith reported fell into the following types: *M. audouini* (20 cases); *M. lanosum* (12 cases); *A. schoenleinii* (3 cases); *Tr. violaceum* (1 case); *M. felinum* (1 case).

*Clinical Data.* An analysis of the patients revealed 28 males (75%) and 9 females (25%).\* The average age of all the patients was  $7\frac{1}{4}$  years. The youngest was  $3\frac{1}{2}$  years and the oldest 17 (case of favus). The duration of the disease varied considerably according to the organism isolated. In patients from which *M. lanosum* was cultured, the disease was present less than 3 months on the average, varying in individuals from 3 weeks to 6 months. In the *M. felinum* case, the duration was said to be 1 week. In the *M. audouini* cases, the average duration was  $8\frac{2}{3}$  months, varying in individual cases from 2 months to 2 years. In the 3 cases of favus, the infection had been present for  $1\frac{1}{2}$ , 2 and 3 years respectively. The patient from which *Tr. violaceum* was isolated stated that the disease was first noticed 5 years before. To 5 patients (3 *M. lanosum*; 1 *M. audouini* and 1 *A. schoenleinii*) Roentgen ray epilation had previously been given. Most of the cases due to an "animal" microsporon, exhibited more inflammatory reaction than the others, although in 3 such cases no erythema was noted and the infections were considered on clinical grounds to be due to *M. audouini*, bearing out the assumption that a botanical diagnosis is not always possible from the clinical characteristics. No typical kerions were present in any case but in several instances, pustulation was noted.

*Wood Light.* In addition to microscopic and cultural studies, hairs either *in situ* or after removal, were examined under the Wood light.† With the exception of 1 case, in which a spontaneous cure apparently occurred, fluorescence of the infected hairs was observed. In all the microsporon infections, the well known bright green effect was noted. In favus, some difficulty was usually met with in distinguishing the infected hairs, which however, on careful examination, could be usually singled out as showing in their entirety, a lighter hue than the normal hairs present and usually fluorescing

\* A review of 108 consecutive cases from the Skin Clinic revealed the incidence between the sexes to be 80 males (77%) and 28 females (23%). Crocker<sup>10</sup> stated that in 600 cases, the disease was 6% more prevalent in boys. Beeson<sup>11</sup> noted that 85% of his cases were males. In Pardo-Castello's series,<sup>12</sup> there was only 1 girl to 31 boys. In this connection it is interesting to note that in ringworm of the adult scalp, Fox and Fowlkes<sup>13</sup> found that in 48 collected cases, 32 females were affected (66%).

† The Wood filter is composed essentially of nickel oxid; the best glass according to Radley and Grant<sup>14</sup> contains 9% of the salt together with silica, barium oxid, potassium oxid and copper oxid. When a source of ultraviolet light is screened with this glass, all the visible rays are absorbed while the ultraviolet rays are transmitted through the filter. Many substances when exposed to the rays, in a dark room, fluoresce in a characteristic fashion.

near the scalp but not with the brilliance of the microsporons. The infected hairs in the case of the *Tr. violaceum* infection showed a bluish-white color not noted in the other varieties. In appearance it resembled the fluorescence of petrolatum, but was differentiated by the negative history of application of grease and from the observation that not all neighboring hairs showed the fluorescence; these hairs also invariably contained fungous material while those not fluorescing were found to be normal. It appears important to remember that in favus and in many of the endothrix trichophytosis the affected hairs are not broken off in short stumps as in the microsporons. Fungous elements usually only invade part of the shaft; consequently only part of the hair fluoresces. However, because of toxic, nutritional or other factors, the remainder of the hair appears lusterless and lighter than normal hair.

The Wood light was an almost indispensable help in determining cure; infected hairs were frequently found when the disease was apparently eradicated to the unaided eye.

**Method of Treatment.** It was felt desirable to standardize the treatment in order to arrive at a fair comparison in the results. Having in mind the time-honored value of iodine, and impressed with the possibilities of the volatile oils, a prescription was concocted containing iodine crystals, thymol and oil of cinnamon  $\bar{a}\bar{a}$  1% in petrolatum. This was found to be slightly irritating. In only 4 cases were different preparations given. In 1 instance, a chlorin compound in petrolatum was used; in another case 1% iodine crystals in petrolatum was prescribed and in 2 instances the treatment consisted of a 10% ammoniated mercury ointment. In all 4 cases, the causal fungus was *M. lanosum*. The parents or attendants were instructed to apply the medicament twice daily preceded by a soap and water shampoo. No manual epilation was practised. The usual hygienic precautions were also outlined. Shaving or clipping of the hair was not stressed although in some instances this was done to facilitate the treatment. The patients were reexamined as frequently as possible and the clinical impression was checked by the Wood light and microscopic and cultural determinations.

**Results.** The uniformity of the results was surprising. All 12 cases due to *M. lanosum* and the case due to *M. felineum* were cured, whereas in none of the cases due to *M. audouinii*, *A. schoenleinii*, or *Tr. violaceum* (24 cases in all) was the disease eradicated. Another patient (not included in this series) spontaneously recovered from an obvious ringworm infection of the scalp; no fungi were demonstrated from the scalp but a coincident tinea circinata of the neck revealed *M. lanosum*. The cases in the *M. lanosum* group were cured on an average of just under 2 months, the shortest time being 3 weeks and the longest time being 3 months. The 4 cases treated with compounds other than the standard formula, all

responded favorably in approximately the average time required for the others. In the case of the patient treated with the chlorin compound, her brother received the standard treatment and both were discharged as cured at the same time. Treatment in the cases due to *M. audouini* was pursued for an average time of  $3\frac{1}{2}$  months, the shortest time being 3 months and longest 5 months. The favus cases were treated for 2,  $5\frac{1}{2}$  and 8 months and the case due to *Tr. violaceum* for 5 months.

*Comments.* The reason for the favorable outcome in the one group is not known. The effect may be due to irritation causing inflammatory changes finally resulting in a biologic cure. Against the premise of a direct fungicidal action was the success achieved in 4 cases of "animal" infection, using different remedies; the failure to cure when other fungi were involved would also speak against a specific medicinal effect.

The lack of response to treatment in the latter group, does not necessarily preclude the possibility of cure without resort to the use of Roentgen rays or thallium acetate. Other remedies and the use of mechanical epilation might be effective, especially when active coöperation of the parents is obtained. There is reason to believe that many such cases have been cured in the past. The results of this investigation, however, indicate a decided difference in the response to therapy between the different species. While no ectothrix (animal) trichophytons were included in this study, it is likely that they also might react favorably to local therapy. Although the results here recorded were uniformly successful insofar as the "animal" microsporons were concerned, the series of cases is too small to state with certainty that all such cases would similarly respond. It is also suggested that reports showing good results from the use of certain drugs applied locally may be justly criticized if cultural studies are lacking, since the favorable outcome might only in part be due to the therapy. Cultural determination of the causative fungus is rarely a routine procedure prior to the treatment of tinea capitis, even in many of the larger institutions. The demonstration of fungi in extemporaneous preparations is usually considered sufficient evidence to proceed with therapy. From the evidence submitted in this report, determinative mycology would appear to be of value from a practical standpoint in treating tinea capitis; *i. e.*, cultures must be obtained!

**Incidence of "Animal" Microsporon Infection.** The mycologic flora appears to vary considerably in different parts of the world.<sup>15</sup> Walker<sup>16</sup> noted the preponderance of microsporon infection in Tinea capitis in Scotland and England while in Italy the trichophytons were chiefly responsible. The "animal" microsporons would appear to be negligible in the British Isles. Sabouraud's statistics<sup>17</sup> reveal that only 3% of his cases were due to *M. lanosum* and a recent report<sup>18</sup> from Bordeaux failed to reveal any "animal" microsporons

in an analysis of 176 patients. Very few complete studies appear to have been made in the United States and Canada (Table 1). Wise<sup>27</sup> stated that 20 years ago, the cases in New York were preponderantly of the non-inflammatory type, considered to be *M. audouini* infections. The situation today has apparently changed although the cases found in institutions or orphan asylums are still usually *M. audouini* infections. In the patients comprising the series herewith reported, the disease was caused by "animal" microsporons in 13 out of 37 cases (35%). This figure, however, is misleading insofar as the ordinary run-of-case in the dispensary is concerned, since only 3 of the *M. audouini* cases should be so included. Excluding institutional cases, it was found that in 65% of the cases the infections were due to "animal" microsporons. It would thus appear likely that a fair percentage of cases of ringworm of the scalp throughout the country are caused by "animal" microsporons.

TABLE 1.—INCIDENCE OF FUNGUS SPECIES CAUSING *TINEA CAPITIS* IN THE UNITED STATES AND CANADA.

Authority.	Location.	Number of cases.	Microsporon audouini (human type).	Microsporon lanosum; Microsporon felinum (animal types).	Other species.
White <sup>19</sup>	Boston	} <i>M. audouini</i> stated to be the predominant organism.		be the predominant	
Corlett <sup>20</sup>	Cleveland				
Wende <sup>20</sup>	Buffalo				
Beeson <sup>11</sup>	Chicago				
Greenwood <sup>21</sup>	Boston	40	25.0%	67.5%	7.5%
Burgess <sup>22</sup>	Montreal	62	32.2%	33.9%	33.9%
Pardo-Castello <sup>12</sup>	Havana	32	.....	100.0%	
Davidson and Gregory <sup>23</sup>	Winnipeg	75	57.0%	43.0%	
Mook <sup>1</sup>	St. Louis	Majority of cases acquired from animals.		50.0%	8.3%
Weidman <sup>24</sup>	Philadelphia				
Jacobson <sup>25</sup>	Los Angeles				
Smith <sup>26</sup>	El Paso				
		..	rarely found	Most frequent	

**Summary and Conclusions.** 1. Thirty-seven patients with *Tinea capitis* were treated with local applications only (*i. e.*, without depilating measures).

2. The results were uniformly good in 13 cases in which the causal fungi were "animal" microsporons.

3. Twenty-four other cases due to *M. audouini*, *A. schoenleinii* and *Tr. violaceum* failed to respond to similar treatment.

4. The ointment used by the majority of the patients in this series is not advanced as a "specific cure" for the cases which responded favorably; it is more than likely that the medicament used might vary considerably in its composition and still be used

successfully in the treatment of infections due to "animal" microsporons.

5. The results of this investigation point to an explanation for the discrepancies in the results which might occur when a given formula is used by different observers in different sections of the country. Likewise, the experience of a physician whose cases are mainly institutional might differ from one whose patients are seen in the dispensary or in private practice, since ringworm of the scalp in orphan asylums and the like is mainly due to *M. audouini* while *M. lanosum* is responsible for a considerable percentage of the latter.

6. *Tinea capitis*, when caused by "animal" fungi, is shown to be curable by local therapy alone in from 3 to 12 weeks. It is suggested that cases in this category should be segregated, for treatment, from the more resistant forms which might require depilating measures by means of the Roentgen rays or thallium acetate. *Cultural determination of the causative fungus would thus appear highly desirable and of practical importance in the management of ringworm of the scalp.*

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## THE ALLEGED INCREASE OF SENSITIVITY OF VASCULAR RESPONSE TO EPINEPHRIN FOLLOWING INJECTION OF PLASMA FROM NEPHRITIC PATIENTS.

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INVESTIGATIONS by Hülse,<sup>1</sup> in Volhard's Clinic, appear to demonstrate that the elevation of blood pressure in patients suffering from nephritis is due to the occurrence of a peptone-like substance in the blood. This substance was found in serum by two methods. The first consisted in the injection of serum into animals and the demonstration that such animals were more sensitive to the pressor action of epinephrin than before treatment with serum. Serum of normal subjects or of patients with essential hypertension did not exhibit this "sensitizing" action. The second method (Hülse and Strauss<sup>2</sup>) consisted in the demonstration that the protein-free trichloroacetic acid filtrate of blood from hypertensive patients with nephritis invariably exhibited an increase in the formalin titrable amino-N after acid hydrolysis (bound amino-N). From these results it was concluded that peptone-like substances appear in the blood of such patients and that it was this fraction which caused the sensitizing action for epinephrin. Neither normal persons nor patients with essential hypertension exhibited any increase in bound amino-N.

The result of the latter of these two methods for demonstrating sensitizing substances has recently been shown to be incorrect by both Jackson, Sherwood and Moore,<sup>3</sup> and more recently by Becker and Herrmann.<sup>4</sup> Neither group of investigators was able to find any relationship between the bound amino-N and the height of the blood pressure.

The biological experiments, however, still remained unquestioned. As the problem is one of importance to the understanding of the mechanism of hypertension, we have thought it desirable to attempt to confirm or disprove Hülse's contention.

**Method.** Most of our experiments were conducted on pithed cats because of their very high sensitivity to epinephrin. The animals were quickly anesthetized with ether, the vagus nerves cut and a tracheal cannula inserted. Blood pressure was recorded by a mercury manometer from the carotid or femoral artery. The skull was trephined and the brain and cord destroyed. Artificial respiration was immediately instituted and no more anesthetic administered. Doses of 1 to 2 cc. of 1 to 2,000,000 epinephrin solution were injected into a femoral vein as soon as the blood pressure had reached a constant level. After repeating the injections a number of times (requiring about  $\frac{1}{2}$  to  $\frac{3}{4}$  hour after discontinuing the ether),



10 to 20 cc. of warm fresh heparinized plasma was slowly injected. The plasma was usually ready for injection 5 to 10 minutes after withdrawal from the patient. Directly following the plasma injection, epinephrin doses were again administered. In some experiments pitressin was then injected in order to enhance the sensitivity of the animal to epinephrin. Just enough was given to produce a very slight rise in the level of blood pressure, and when the pressure had again fallen nearly to normal, epinephrin was again given.

Experiments were also performed as outlined, but employing etherized cats with the central nervous systems intact.

Besides native plasma, alcohol extracts of plasma were prepared by a method published elsewhere.<sup>5</sup> It consisted in precipitation of proteins and lipids with alcohol, removal of the alcohol under vacuum and freezing the remaining fat from the extract. A clear water extract of the plasma resulted. Ultrafiltrates of plasma were also prepared by three different methods: (1) Dialysis through collodion thimbles. (2) Suction through collodion coated porcelain pear-shaped thimbles. (3) High pressure filtration. (Pfaltz and Bauer apparatus.)

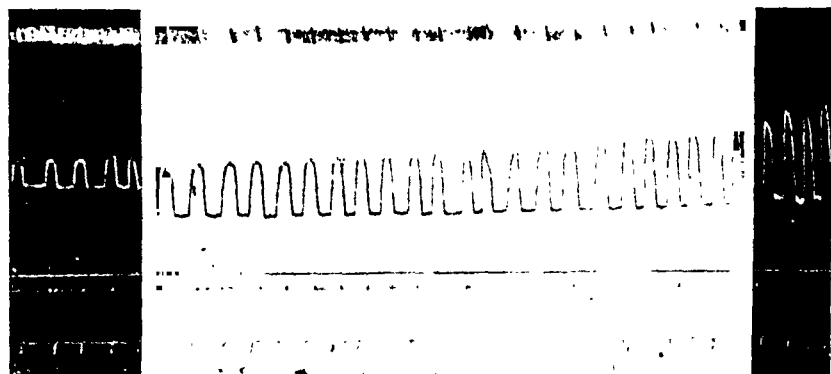


FIG. 1.—Example of the progressive increase in response of the pithed cat to injections of 2 cc. of 1 to 200,000 epinephrin. Ether removed 45 minutes before the injections were begun. Initial pressure, 62 mm. Hg.

**RESULTS.** Repeated injection of epinephrin into pithed cats led to a progressive increase in the vascular response to it (Fig. 1). This action of epinephrin was first noted by Levy<sup>6</sup> and has been studied in detail by Weyman and Lutz.<sup>7</sup> Animals with intact nervous systems also exhibit the phenomenon (Fig. 2). It is, therefore, evident that any increase in sensitivity must be corrected by subtraction of the increment which normally accompanies repeated injections of epinephrin. This Hülse did not do.

In no experiment (22 experiments) did we observe an increase in the sensitivity of the pithed animal to epinephrin following the intravenous injection of from 10 to 20 cc. of plasma, whether the plasma originated from patients with severe nephritic hypertension (8), essential hypertension (6) or normal subjects (3). Negative results were also obtained on animals in which the central nervous system was intact.

Administration of pitressin increases the sensitivity of the animal to epinephrin two to fourfold. In those animals with enhanced susceptibility, administration of plasma was also unsuccessful in

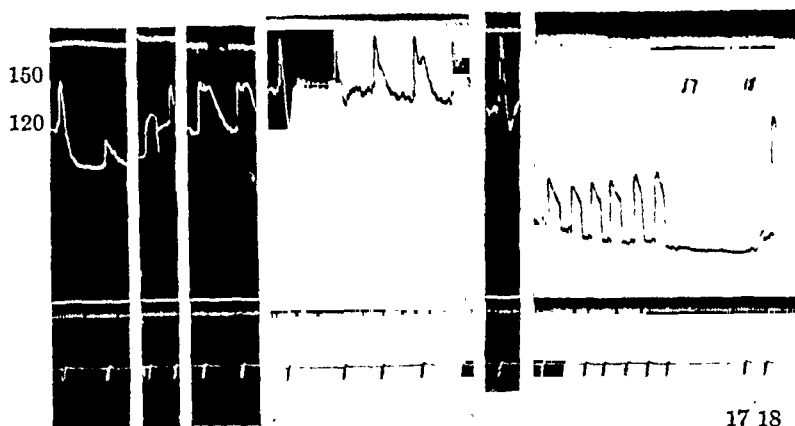


FIG. 2.—Sensitization to epinephrin with and without central nervous system intact. Repeated injections of 2 cc. of 1 to 100,000 epinephrin. At 17, extract of 20 cc. plasma of a severe hypertensive nephritic (blood-pressure, 216/126) was injected. At 18, a small dose (1 cc. of 1 to 25 dilution) of pitressin was given, followed by the usual epinephrin dose. Initial pressure, 120 mm. Hg.

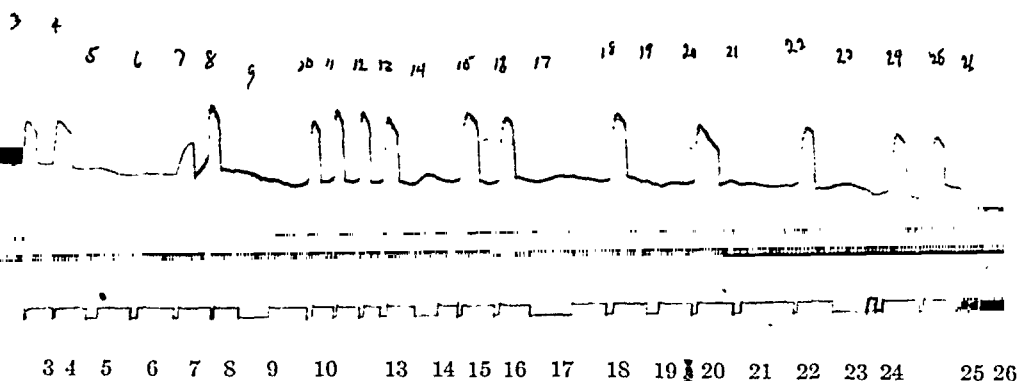


FIG. 3.—Sensitivity to epinephrin following plasma and plasma extract injection in pithed cat. 3, 4, 2 cc. of 1 to 100,000 epinephrin. 5, Extract of 5 cc. plasma of severe nephritic with hypertension (blood-pressure, 200/122). 6, Extract of 30 cc. plasma of same patient. 7 and 8, Epinephrin. 9, Extract of 15 cc. plasma from same patient. 10 to 13, Epinephrin. 14, 10 cc. plasma from same patient. 15 and 16, Epinephrin. 17, 10 cc. plasma from same patient. 18, Epinephrin. 19, Extract of 15 cc. plasma from same patient. 20, Epinephrin. 21, Extract of 20 cc. of plasma from severe essential hypertensive (blood-pressure, 220/130). 22, Epinephrin. 23, Extract of 20 cc. plasma from nephritic without hypertension (blood-pressure, 120/60). 24 and 25, Epinephrin. 26, Extract of 18 cc. plasma from severe essential hypertensive Expt. No. 110 (blood-pressure, 52 mm. Hg.).

further increasing it. Neither did ultrafiltrates (9) nor alcoholic extracts (19) of plasma exhibit the slightest effect on epinephrin susceptibility (Fig. 3) regardless of the origin of the plasma.

**DISCUSSION.** Native plasma, alcoholic extracts and ultrafiltrates thereof do not alter the responsiveness of the vascular system to epinephrin either in pithed cats or etherized normal cats. We, therefore, find no basis for Hülse's claim that substances which enhance the vascular action of epinephrin are present in the blood of hypertensive nephritic patients. It is possible that he mistook the increased susceptibility to epinephrin which normally accompanies its repeated administration for an effect due to plasma.

These experiments appear to remove the support which the pharmacologic method offered to Hülse's theory of hypertension. We have already referred to the fact that Hülse and Strauss<sup>2</sup> chemical evidence as to the existence of peptone in the blood of hypertensive nephritic patients has not received confirmation by other investigators.<sup>3,4</sup>

**Conclusions.** Hülse's theory that the hypertension in nephritis is due to occurrence of peptone-like substances in the blood which are able to sensitize the bloodvessels of animals to epinephrin receives no support from this investigation. It was shown that heparinized plasma, ultrafiltrates and alcohol extracts thereof do not increase the vascular response of cats to epinephrin regardless of whether the plasma originates from patients with nephritis, with hypertension, essential hypertension or normal subjects.

Epinephrin repeatedly injected normally increases the vascular response of anesthetized animals to it. This fact may partially explain Hülse's results.

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#### A NOTE ON PARENTERAL LIVER THERAPY IN STREPTOCOCCUS PNEUMONIA.

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LIVER extract injected intramuscularly and intravenously causes a leukocytosis and a relative increase in the neutrophils. This was shown by Foran, Sheaff and Trimmer<sup>1</sup> in the successful treatment of 5 cases of agranulocytic angina. Murphy<sup>2</sup> reported finding a leukocytosis, as well as an increase in hemoglobin and erythrocytes, in pernicious anemia following injections of liver extract.

Meyer, Middleton and Thewlis<sup>3</sup> studied 4 apparently normal persons and 3 with abnormal conditions. Injections of liver were given, then frequent white blood counts made. In all, there was a definite increase in the white blood cells. In 1 case, the leukocyte count increased following the injections of liver extract, before and after splenectomy. They conclude that parenteral liver extract stimulates the bone marrow and other sources of the cellular elements of the blood.

Middleton and Gibbon<sup>4</sup> in a study of 164 cases of pneumonia in hospital practice, 64 of which died and 100 recovered, found the average leukocyte count of the recovered cases was 21,046, and of those who died 14,700. They expressed the opinion that the absence of leukocytosis is unfavorable, and leukopenia an ominous sign in pneumonia. A high total leukocyte count, especially 20,000 or above, is reassuring.

It seems reasonable, therefore, to expect that in view of the published data on the effect of liver therapy on leukopoiesis, it would be of value in cases of pneumonia with leukopenia or low leukocyte count. The object of this report is to place on record a description of 2 cases of streptococcus lobar pneumonia which showed striking improvement following parenteral liver therapy.

**Case Abstracts.** CASE 1.—R. F., aged 45, Swedish-American, milk dealer and farmer, had previous attacks of pneumonia in 1920 and 1926. Family history negative, except that father and mother, on adjoining farm, were just recovering from pneumonia. He was first seen at his home, February 6, 1934, complaining of general malaise, fever and pains in the right chest. Many fine râles were heard in the right axilla. Leukocyte count was 16,000 (Table 1). On the morning of February 9, he was definitely worse, very toxic, coughing a small amount of bloody sputum, and was admitted to the Meriden Hospital. The next day, the fifth day of his illness, he was gravely ill, irrational, and with a lowered leukocyte count. That afternoon, liver injections were started, and by the end of the sixth day, he was definitely better and continued to improve. His temperature receded by lysis, reaching normal on the eleventh day.

**Physical Examination.** A very well nourished, adult, white male, slightly confused mentally. Respirations were rapid, skin flushed and cyanotic. Chest showed definite pneumonia with many fine crepitant râles in the right axillary region. Heart sounds were fast but normal. Abdomen was slightly distended.

**Laboratory Examination.** Blood counts (Table 1). Sputum was bright red and on direct smear showed long chains of streptococci. Cultures on blood agar showed Beta hemolysis. Negative for Type I, II, III and VII pneumococci (Neufeld). Urine, 1.023, negative albumin and sugar, rare red blood cell. Report of Roentgen ray taken the twelfth day showed consolidation of the upper and middle lobe of the right lung undergoing resolution. No fluid present.

**Treatment.** Oxygen therapy was started on the third day and given through the seventh day. Liver extract injections (intramuscular) were started on the fifth day of the disease. Ammonium chlorid was given in small doses in the beginning; and on the fifth and sixth days, Digalen (Roche) and strychnin were given hypodermically to support the circulatory system.

TABLE 1.—BLOOD FINDINGS.

Date.		Case 1.				Urine 24 hours (in cc.).
		Liver extract (cc.)	W. B. C. in thousands.	Polymor.	Temp.	
2-7-1934			16.0	91%	103°	
2-9-1934			9.2	SS	104	1600
2-10-1934	9 A.M.		8.2		103.6	500
	4 P.M.	3				
	10 P.M.	3				
2-11-1934	5 A.M.	3				3400
	9 A.M.		27.8		102	
	10 A.M.	3				
	3 P.M.		25.4			
	10 P.M.	4				
2-12-1934			26.8	S4	101	1050
2-13-1934			25.0		100.2	1300
2-14-1934			24.4		100	950
2-15-1934			20.0		100	1750

1 cc. is equivalent to 50 gm. of fresh liver (Endo).

		Case 2.				Urine 24 hours (in cc.).
			W. B. C. in thousands.	Polymor.	Temp.	
7-17-1934			10.4	75%	104.2°	700
7-18-1934			8.2	72	104	300
7-19-1934	10 A.M.	2	5.2	68	105	600
	4 P.M.		7.2	67		
	10 P.M.	2				
7-20-1934	9 A.M.		6.8	70	105.4	850
	10 A.M.	4				
	10 P.M.	4				
7-21-1934	10 A.M.	4	6.4	67	104.2	1000
7-22-1934	10 A.M.	4			104.4	700
7-23-1934	10 A.M.	4	7.2		103.8	1050
7-24-1934			8.4		103	1450
7-26-1934	10 A.M.		4.6		102.6	1500
7-27-1934	10 A.M.	4			100.2	1350
7-28-1934			12.2		99.6	
8-1-1934			7.2	68	98.8	

CASE 2.—W. L., aged 21, graduate nurse, family and personal history negative, was taken ill on July 15, 1934, and admitted to the hospital on the third day of her illness, complaining of general malaise, fever and slight cough. The fourth day, a Roentgen ray of her chest revealed a pneumonic process in the left outer middle area. No physical signs were present until the seventh day when many fine râles were heard over the same area. Temperature ranged from 101° F. in morning to 105.4° F. in afternoon, the highest point being reached on the sixth day. Her temperature gradually receded with improvement in her general condition, and on the fifteenth day, the temperature was normal.

*Physical Examination.* Patient slightly built, poorly nourished, mentally clear, no dyspnea or cyanosis. Face was flushed, throat slightly reddened, lungs clear, no râles heard. Heart sounds were regular, systolic murmur at the apex. This was an old lesion and had been noted 3 years before this illness. Abdomen and extremities were normal.

*Laboratory Examination.* Blood counts (Table 1). Sputum was scanty in amount, yellow, negative for tubercle bacilli and for Type I, II, III and VII pneumococci (Neufeld). Direct smear showed many long chains of streptococci. Cultures on blood agar showed Beta hemolysis. Blood Wassermann was negative. Agglutination tests of blood serum were negative for typhoid, paratyphoid A and B, Weil-Felix and undulant fever.

*Treatment.* Ammonium chlorid in small doses. Liver extract injected daily from the fifth to the ninth days inclusive and again on the twelfth day (see table).

**Discussion.** The injection of liver extract was tried in the first case of pneumonia because of the drop in leukocyte count from 16,000 to 8200 in 3 days. When liver extract was started, this patient was seriously ill, in a light stupor, high fever, able to take very little nourishment, and voided 500 cc. of urine in 24 hours. The prognosis seemed poor. Sixteen cc. of liver extract (equivalent of 800 gm. of fresh liver) were given intramuscularly between 4 P.M. of the fifth day and 4 P.M. of the sixth. The leukocyte count rose from 8200 to 27,800. The patient improved. He voided 3400 cc. of urine in 24 hours, and although still confused mentally, the stupor was less and the fever lower. The leukocytes remained above 20,000 until the tenth day of his illness. The fever came down by lysis and there were no complications. He was discharged from the hospital on the fifteenth day.

The leukocyte count in the second case, on the third day of illness was 10,400 and had dropped to 5200 on the fifth day. Daily liver extract injections were started on the fifth day and given for 5 days. The general condition of the patient was greatly improved, and the average leukocyte count was 7000. No injections were given on the tenth, eleventh and twelfth days of the disease. The leukocyte count on the twelfth day was 4600. Four cc. of liver extract were given on the thirteenth day, and on the fourteenth day, the count rose to 12,200. In 3 more days the count dropped to 7000. The temperature was normal by this time, the patient improved rapidly and no complications occurred.

Differential counts coincided with the number of leukocytes. An increased leukocyte count was accompanied by a relative increase in the neutrophils. The number of white blood cells seemed to be a sufficient index of the patient's condition.

The diagnosis of streptococcus pneumonia was based on the report of large numbers of streptococci in the smears and cultures from the sputum and the negative result for pneumococcus Types I, II, III and VII and the absence of pneumococci in smears of sputum. The sputum in one case contained bright red blood and in the other it was yellow. In neither was it the typical rusty or brown sputum characteristic of a pneumococcal infection.

In studying the hospital chart, it was interesting to note that the output of urine was below normal just before the liver therapy was instituted, and greatly increased after it was given in each case (see table). The first patient averaged an intake of 3000 cc. of fluids a day and the second 2500 cc. daily.

**Summary.** 1. The effect of parenteral liver extract in the 2 cases of streptococcus lobar pneumonia described, suggests that it is a valuable therapeutic agent. Recovery took place in both cases

with no complications, the temperature returning to normal by lysis.

2. Due to the success of liver therapy in these cases, it should be considered in any type of pneumonia with a low or receding leukocyte count.

3. Daily or frequent leukocyte counts are important indices in the progress of a pneumonia patient.

4. The daily output of urine was increased following the liver treatment.

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### THE ETIOLOGY OF "ALCOHOLIC" POLYNEURITIS.\*

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SINCE Lettsom<sup>1</sup> first described "alcoholic" polyneuritis, in 1787, a direct neurotoxic effect of alcohol has been considered to be the causative agent. Six years ago, however, Shattuck<sup>2</sup> suggested that this disease was "caused chiefly by failure to take or to assimilate food containing sufficient quantity of vitamin B" and "might be properly regarded as beriberi." Meyer,<sup>3</sup> Wechsler<sup>4</sup> and a number of other clinicians have concurred in this point of view, without, however, advancing any further evidence for it. Minot, Strauss and Cobb<sup>5</sup> have discussed the subject, pointing out the clinical and pathologic similarities between the polyneuritis associated with alcoholism and that of beriberi, and noting the fact that over one-fourth of their 57 patients with undoubted "alcoholic" polyneuritis also had pellagra, a disease which is now generally believed to be the result of dietary deficiency. Dietary histories of 43 of their patients showed that 41 of these individuals had partaken of grossly inadequate diets for prolonged periods of time. Twenty-one patients had gastric anacidity and 15 had gastric hypoacidity, which states might well have interfered with the proper assimilation of nutriment from the gastro-intestinal tract. While these facts undoubtedly add to the concept that "alcoholic" polyneuritis is

\* A preliminary report of this study was presented before the American Society for Clinical Investigation at Atlantic City, N. J., April 30, 1934.

the result of dietary deficiency, they fail to prove the case against a direct neurotoxic effect of alcohol upon peripheral nerves.

The work of Spies and DeWolf<sup>6</sup> on "alcoholic" pellagra suggested that a method similar to theirs might be employed in making observations upon patients with "alcoholic" polyneuritis. If alcohol has a direct neurotoxic effect on peripheral nerves in the amounts consumed by the individuals who develop polyneuritis, then this condition should become progressively worse if the use of alcohol in similar amounts is continued. Certainly no amelioration of the polyneuritis should be expected in patients who continue the excessive use of alcohol.

*Procedure.* Ten patients with "alcoholic" polyneuritis not complicated by severe febrile infections or decubitus were selected for study. Data concerning these individuals are summarized in Table 1. By careful questioning, the usual daily intake of spirituous liquors was determined in each case. Such an amount of pure blended whisky (from 1 pint to 1 quart) was then administered daily to each patient throughout the period of study. At the same time each patient was placed upon a dietary régime which included 2 eggs, 1 pint of milk, 225 gm. of beef or lamb, 240 cc. of orange juice and 4 servings or about 240 gm. of green vegetables daily, as a *minimum*. Other foods were added to make up the necessary total caloric intake for each individual. Eighteen grams of Vegex, or 30 Harris yeast-vitamin tablets, or 90 gm. of dried brewers' yeast were administered daily by mouth; 10 cc. of solution liver extract, Lilly (N.N.R.),\* were injected intramuscularly each week, and 10 cc. of a vitamin B concentrate\* were injected intramuscularly daily in each patient.

From evidence in the literature, it appears that neural changes may result from dietary deficiencies other than a lack of vitamin B<sub>1</sub>. Mellanby<sup>7</sup> suggests that vitamin A is necessary for the integrity of the nervous system, and Gildea, Kattwinkel and Castle<sup>8</sup> produced neural lesions in dogs by the use of diets deficient in the vitamin B complex. Cowgill *et al.*<sup>9</sup> have reported demyelination of peripheral nerves in dogs deprived only of vitamin B<sub>2</sub> (G) and also in dogs maintained on the Goldberger 195 diet.<sup>10</sup> The occurrence of spinal cord and peripheral nerve lesions in pernicious anemia<sup>11</sup> suggests the possible rôle of a lack of the "liver extract" factor. The influence of malabsorption from the intestinal tract in the production of polyneuritis has recently been reviewed.<sup>12</sup> These facts led to the employment of diets adequate in all respects, and, in addition, to the parenteral administration of both vitamin B concentrates and liver extract.

When this study was commenced it was found that even endless patience and skill on the part of the nursing staff was insufficient to make these patients eat the requisite food, owing to the anorexia

\* Kindly supplied by Eli Lilly and Company, Indianapolis, Ind.



TABLE 1.—SUMMARY OF NEUROLOGIC EXAMINATIONS BEFORE AND AFTER TREATMENT WITH HIGH VITAMIN DIET, PARENTERAL VITAMIN B AND LIVER EXTRACT AND LARGE QUANTITIES OF WHISKY UPON 10 PATIENTS WITH "ALCOHOLIC" POLYNEURITIS.

	51 yrs., M.		32 yrs., M.		41 yrs., F.		37 yrs., M.		12 yrs., M.		38 yrs., M.		36 yrs., F.		42 yrs., F.	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Age and sex of patient	51 yrs., M.	32 yrs., M.	41 yrs., F.	37 yrs., M.	12 yrs., M.	38 yrs., M.	36 yrs., F.	42 yrs., F.								
Duration of polyneuritis (before treatment)	10 weeks	2 weeks	8 mos.	1 quart 120 days	9 weeks	1 pint 63 days	5 mos.	1 pint 78 days	1 week	1 quart 24 days	5 weeks	1 pint 32 days	5 years	1 pint 115 days	9 weeks	1½ pints 63 days
Daily intake of whisky (during treatment)	1 quart 33 days	1 quart 120 days	1 quart 90 days	1 quart 90 days	1 pint 63 days	1 pint 63 days	1 pint 78 days	1 pint 78 days	1 quart 24 days	1 quart 24 days	1 quart 14 days	1 pint 32 days	1 pint 115 days	1 pint 115 days	1½ pints 63 days	1½ pints 63 days
Duration of treatment	33 days	120 days	90 days	90 days	63 days	63 days	78 days	78 days	24 days	24 days	14 days	32 days	115 days	115 days	63 days	63 days
Time of examination with regard to treatment	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Strength, arms and hands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep reflexes, arms	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin sensation, arms and hands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vibration sense, upper	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Strength, legs and feet	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Knee jerks	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ankle jerks	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plantar responses	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin sensation, legs and feet	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Position sense, toes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vibration sense, tibiae	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tenderness of calves	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Standing*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Walking*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mental state†	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

N signifies normal. 0 signifies absent. The number of minus or plus signs signifies the degree of diminution or increase, respectively, in the sign.  
 \* When standing or walking are represented by 0, this signifies inability to stand or walk.  
 † Under mental state is indicated the Korsakow type of psychosis.

so common in "alcoholic" polyneuritis. Accordingly, a decision was made to abandon the study in any individual who would not eat. It was, therefore, made clear to each of the patients that if he did not eat all the food presented, the customary postprandial whisky would not be forthcoming. Need to carry out this threat occurred but once during the course of the 1918 meals served to the 10 patients.

*Results.* The results obtained during the period of observation are summarized in Table 1. Examination of this data shows that, without exception, the polyneuritis of each of the 10 patients was improved during the constant administration of large amounts of whisky. Clinical observation of these individuals revealed no differences in the rapidity or degree of recovery of the polyneuritis as compared to similar patients treated without whisky.

*Discussion.* It is apparent from the above that ingestion of alcohol had no demonstrable neurotoxic effect on peripheral nerves when given in amounts up to a quart a day, in patients who were partaking of an adequate diet and receiving injections of liver extract and vitamin B concentrates. Nevertheless, it remains theoretically possible that even smaller quantities of alcohol so administered as to raise the blood alcohol to a high concentration might cause damage to the peripheral nerves. It is a matter of commonplace observation that a pint of whisky ingested at one time on an empty stomach will produce cerebral effects far in excess of those caused by twice that quantity of alcohol ingested in frequent small amounts over a period of many hours. However, polyneuritis has not been reported following acute alcoholism except when a definite poison such as triorthocresyl phosphate<sup>13</sup> has been ingested with the alcohol, in which case the clinical features of the polyneuritis are quite different from those of the polyneuritis associated with chronic alcoholism. Furthermore, "alcoholic" polyneuritis has not been encountered, at least in recent years, among a university group of about 7500 young men, some of whom, there is reason to believe, not infrequently ingest excessive quantities of alcohol during such a relatively short period of time that marked cerebral effects are produced, including unconsciousness.\*

Many years ago, Eijkman<sup>14</sup> suggested that foods such as polished rice, being overrich in starch, produced a substance in the intestine which was poisonous to nerve cells and for which the outer layers of rice acted as an antidote. One may similarly argue today that alcohol is poisonous to nerve cells unless there is a sufficient amount of vitamin B or some other dietary factor present to act as an antidote. Such speculation must remain unanswered for the present.

The observations reported here do not in any way eliminate the possibility that some impurity which might have been present in

\* Personal communications from the various physicians in charge of the health of this group of young men.

the beverage alcohol consumed by these patients before the onset of polyneuritis was responsible for the nerve lesions. However, the data presented clearly indicate that the administration of pure blended whisky in quantities varying from 1 pint to 1 quart daily in no way prevents the relief of "alcoholic" polyneuritis when the patients are adequately nourished.

The clinical and pathologic aspects of the polyneuritis associated with alcoholism are essentially the same as those of the polyneuritis of beriberi. The dietary histories of the patients and the common association with easily recognizable deficiency diseases, such as pellagra, make it appear probable that "alcoholic" polyneuritis is a dietary deficiency disease similar to beriberi. The high incidence of gastric secretory defects in these patients suggests that poor assimilation of nutriment from the gastro-intestinal tract plays a rôle in conditioning the deficiency state.

**Summary and Conclusions.** Ten patients suffering from "alcoholic" polyneuritis were allowed to continue their customary daily intake of spirituous liquor on condition that they consumed a well-balanced, high vitamin diet supplemented with yeast or its products. They were further given vitamin B concentrates and liver extract by parenteral injection in order to obviate any possible disturbance in absorption present in the patients or resulting from their use of alcohol. Improvement in the polyneuritis occurred in every instance.

The conclusion is drawn that "alcoholic" polyneuritis does not result primarily from a direct neurotoxic effect of alcohol, but is probably the result of a dietary deficiency, possibly conditioned in some cases by disturbed gastro-intestinal function. "Alcoholic" polyneuritis may be regarded as similar to the polyneuritis of beriberi and treated accordingly.

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# SEDIMENTATION TIME AS AN AID IN DIFFERENTIATING ACUTE APPENDICITIS AND ACUTE SALPINGITIS.

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THE rapid sedimentation of erythrocytes has been observed in inflammatory diseases. As a diagnostic aid in differentiating these diseases, the consensus of opinion is that it offers nothing more than the leukocyte and differential counts.<sup>1</sup>

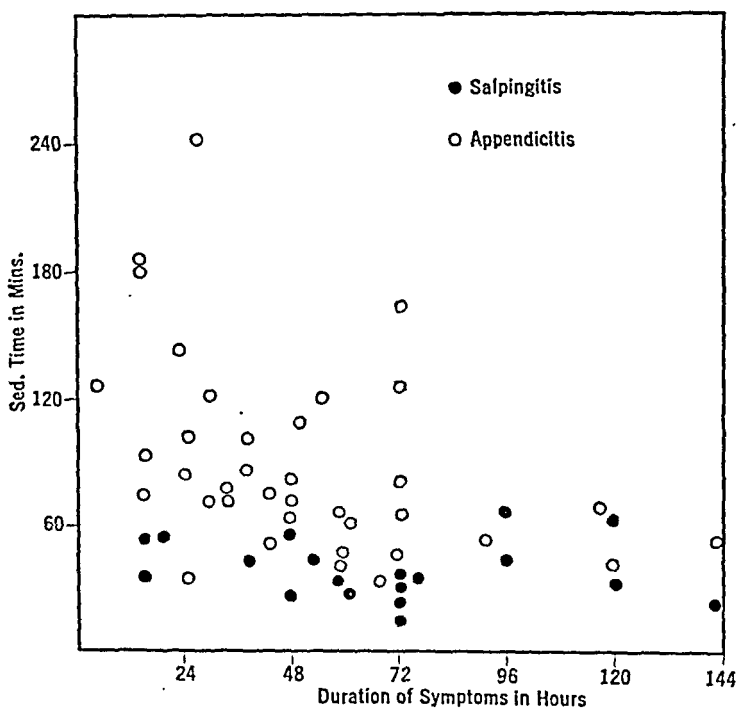


CHART I.—Duration of symptoms in hours.

In a study of 19 cases of acute salpingitis and 38 cases of acute appendicitis, there is a definite suggestion that the sedimentation time may be of some value in differentiating these two conditions, *if the duration of symptoms when the test is made is taken into consideration.* During the first 24 or even 48 hours after the onset of symptoms, the sedimentation time is apt to be shorter in acute salpingitis than in acute appendicitis; an occurrence that is not

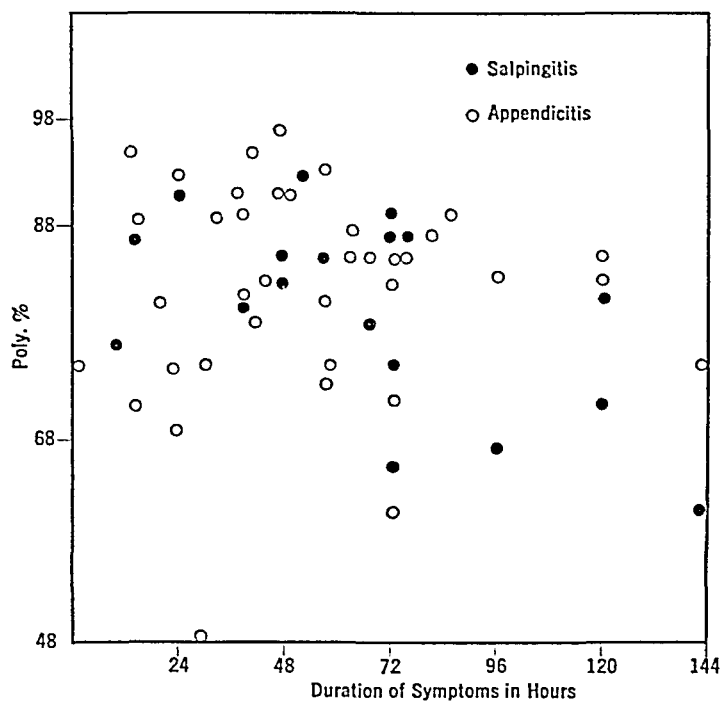


CHART II.—Duration of symptoms in hours.

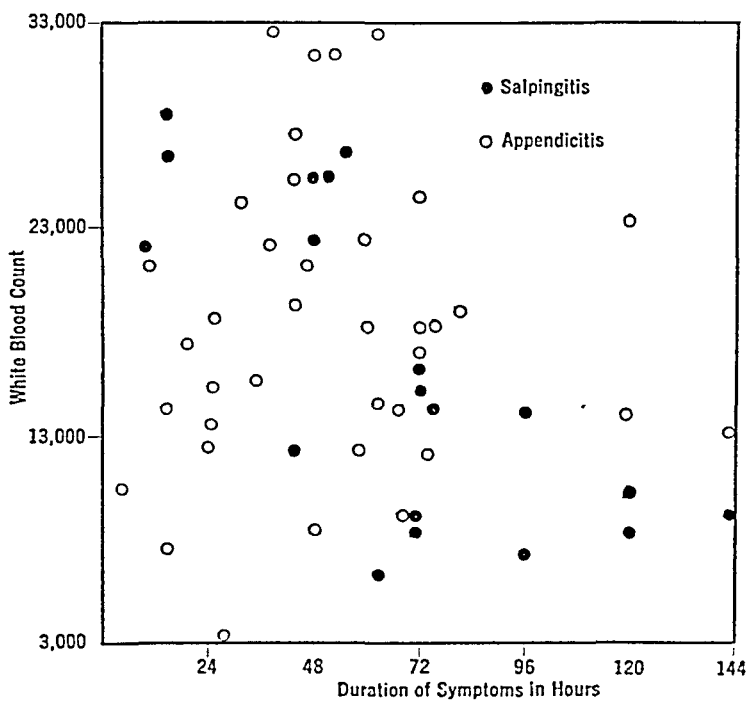


CHART III.—Duration of symptoms in hours.

unfailing, but frequent enough to be given consideration, as it is more uniform than either the leukocyte count or the differential.

These cases were not selected, except that care was taken to exclude other causes for alteration in the sedimentation time; such as pregnancy, tuberculosis, hemorrhage, anemia, the puerperal state, syphilis, and coincidental infection of other organs. For the estimation of the sedimentation time, the Linzenmeier method was used: 0.4 cc. of a 5% sodium citrate solution was drawn into a 2 cc. Record syringe. From a vein sufficient blood was drawn to make

TABLE 1.—APPENDICITIS.

No	Name.	Dur. of symptoms (in hrs.)	Sed. time (in mins.)	W. B. C. (thousand per c.mm.)	R. B. C. (millions per c.mm.)	Poly. per cent.	Operative findings.
1	F. R. Y.	2	126	10.2	...	75	Ac. appendicitis
2	J. R.	14	91	21.5	4.1	94	Ac. appendicitis
3	S. P. P.	15	186	17.5	5.0	88	Ac. appendicitis
4	R. C. F.	16	180	14.8	...	75	Ac. appendicitis
5	O. H. C.	16	71	7.6	...	71	Ac. appendicitis
6	M. E. B.	22	100	12.8	...	80	Ac. appendicitis
7	D. R. C.	24	150	16.8	...	68	Ac. appendicitis
8	W. A. C.	24	37	15.2	4.8	77	Ac. appendicitis
9	W. L.	24	88	13.9	...	74	Gang. appendicitis
10	C. J.	29	120	13.5	4.8	48	Ac. appendicitis
11	J. W.	30	240	24.0	...	92	Ac. appendicitis
12	S. T.	30	77	14.2	...	85	Gang. appendicitis
13	H. G. M.	32	70	15.6	4.0	75	Perf. appendicitis
14	S. M. M.	36	131	33.5	...	89	Gang. appendicitis
15	J. M. S.	36	70	22.2	...	89	Ac. appendicitis
16	D. R.	39	84	27.0	...	94	Perf. appendicitis
17	J. F. B.	42	103	21.0	...	81	Gang. appendicitis
18	R. O. G.	40	51	19.6	5.1	90	Ac. appendicitis
19	G. C. P.	45	75	25.5	...	83	Perf. appendicitis
20	A. M. C.	48	85	8.6	...	91	Ac. appendicitis
21	H. I. P.	48	63	31.3	4.2	90	Ac. appendicitis
22	E. L. C.	48	71	31.0	...	96	Perf. appendicitis
23	G. W.	55	41	12.0	3.8	81	Perf. appendicitis
24	B. A.	56	115	22.4	...	72	Gang. appendicitis
25	P. J. B.	58	110	51.3	...	93	Gang. appendicitis
26	R. E. L.	56	44	17.0	5.1	75	Perf. appendicitis
27	W. H. M.	60	61	14.2	...	87	Perf. appendicitis
28	A. S. F.	60	66	14.4	4.6	85	Perf. appendicitis
29	C. M.	72	48	18.0	...	85	Gang. appendicitis
30	D. L. J.	72	80	12.8	...	82	Perf. appendicitis
31	H. L.	72	33	24.8	4.5	85	Gang. appendicitis
32	E. R.	72	67	17.1	5.4	60	Ac. appendicitis
33	V. S.	72	163	9.2	4.7	71	Ac. appendicitis
34	P. M. W.	72	126	18.2	...	87	Gang. appendicitis
35	C. L. D.	88	58	19.4	...	88	Gang. appendicitis
36	D. P.	120	41	23.6	4.3	85	Perf. appendicitis
37	P. T.	120	67	14.0	...	84	Gang. appendicitis
38	W. W.	144	41	13.0	4.2	74	Perf. appendicitis
Average		50.2	70	18.9		81.5	

NOTE.—All these cases had negative Wassermann tests, and were negative for tuberculosis clinically.

2 cc. of the mixture. This was mixed then transferred to a 1 cc. serologic pipette graduated in 0.01. The time in minutes for the erythrocyte column to reach the 0.18 mark was recorded.

TABLE 2.—SALPINGITIS.

No	Name.	Dur. of symptoms (in hrs.).	Sed. time (in min.).	W. B. C. (thousands) (per c.mm.).	R. B. C. (millions) (per c.mm.).	Poly. per cent.
1	N. R. B.	14	56	22.4	4.8	77
2	L. E. J.	16	30	28.2	4.0	87
3	M. F. G.	22	58	28.6	5.1	91
4	M. M. P.	40	46	12.0	4.5	80
5	G. A. W.	48	28	22.8	4.0	83
6	N. L. A.	48	59	25.0	4.6	85
7	V. H. L.	52	42	26.9	4.4	92
8	M. E. T.	56	31	25.0	4.1	85
9	L. C.	60	30	6.2	4.4	77
10	M. P.	72	19	9.0	4.2	74
11	L. J. P.	72	28	17.2	4.3	89
12	I. McG.	72	34	8.2	4.8	65
13	E. G. B.	72	35	16.8	4.3	87
14	A. W.	76	45	14.6	4.9	87
15	E. W.	96	77	7.4	4.6	66
16	E. F. G.	96	46	15.4	4.0	83
17	S. B. G.	120	65	10.4	4.3	71
18	A. M. A.	120	38	8.4	4.9	81
19	W. W.	144	27	13.0	4.2	74
Average		68	41.7	16.7		80

NOTE.—All these cases showed acute salpingitis at operation, had negative Wassermann tests and were negative for tuberculosis clinically.

It will be observed in Chart I that in the cases of acute appendicitis, the sedimentation time is likely to be prolonged well over an hour within the first 48 hours after the onset of symptoms. After the 48 hours, there is a definite tendency for the sedimentation time to be shortened. On the other hand, in the cases of acute salpingitis, the time is not so prolonged, even in the 24-hour period from the onset of symptoms.

In accounting for this difference in the behavior of the sedimentation time in the two conditions, there can be no assumption that the difference in the infecting organism can be a factor. It may, however, be due to difference in the two organs as regards their function and nerve supply. The appendix is supplied by both sympathetic and parasympathetic nerve fibers. Gastro-intestinal symptoms occur for some time before there is any tenderness localized over the region of the appendix. Furthermore the appendix is a vestigial organ which is capable of only slight distensibility before it begins to cause symptoms. The Fallopian tube has only sympathetic nerve fibers;<sup>2</sup> it is a functioning organ which is capable of relatively great distensibility before causing symptoms. In Chart I it is shown that with the duration of the infection the sedimentation time becomes shortened in the case of acute appendicitis, and it may

be inferred that this is probably what happens in acute salpingitis. But in the case of salpingitis, the infection progresses further before giving symptoms. Therefore, the sedimentation time in acute salpingitis is shorter in the first 24 and 48 hours after onset of symptoms, because the infection had been there many hours before it began to cause symptoms.

Charts II and III are presented only to show that the leukocyte and differential counts are nothing like as uniform as the sedimentation time in differentiating the two diseases.

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### ACUTE EOSINOPHILIC LEUKEMIA.

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THE available literature contains reports of 3 instances of acute leukemia characterized by a preponderance of eosinophils in the peripheral blood and in tissue infiltrations.<sup>1,2,3</sup> The following case, with detailed postmortem observations is of interest because of the apparent rarity of the condition.

**Case Report.** D. K., a 17-year-old schoolgirl, was admitted to the Rochester Municipal Hospital on April 21, 1934. For the past 2 or 3 months small areas of discoloration of the skin had been noted from time to time. During this period her parents had noted gradually increasing pallor and limitation of exercise tolerance. For about 10 days there had been constant headache and for 7 days a purpuric eruption over the entire body. For 24 hours before admission there had been fever and prostration, with cyanosis and progressive dyspnea. The family history and the past history contributed nothing of importance.

At the time of examination, the rectal temperature was 39° C.; respiration 56 per minute. The patient was semi-comatose with marked cyanosis of the face, lips and nail beds. The skin of the face, trunk and extremities was covered with an ecchymotic and petechial eruption. Numerous petechiae were scattered over the mucous membranes of the mouth and the conjunctivæ. A few small discrete nodes were felt on either side of the neck and in the right axilla, but there was no other glandular enlargement. Loud, moist râles were heard in both lungs. The heart was not enlarged to percussion; the sounds were very faint and of poor quality. The pulse was imperceptible and the blood pressure could not be obtained. The spleen and liver were not palpable. The tendon reflexes could not be obtained.

White blood cells numbered 130,000 per c.mm. The differential count was as follows: neutrophilic stab forms, 0.2%; segmented neutrophils, 9.8; eosinophilic stab forms, 1; segmented eosinophils, 67.6; neutrophilic



myelocytes, 2.6; myeloblasts, 16.6; lymphocytes, 2.2. The size and number of the granules in the eosinophils varied considerably; two and three lobed nuclei predominated. In counting 500 leukocytes, one nucleated red blood cell was encountered. There was almost complete absence of platelets in the smear. The blood Wassermann reaction was negative. It is unfortunate that there was no opportunity for more detailed laboratory studies. It was apparent from the appearance of the skin and mucous membranes that there was a moderately severe anemia.

The patient was admitted to the hospital at 2 A.M. and died 6 hours later.

**Autopsy** (Dr. Fischer, 2 hours after death). The body was that of a well developed and nourished white female. There were small petechiæ in the scleræ and conjunctivæ, the skin over the entire body, and at the tip of the tongue and in the mucous membranes of the mouth. The gums were pale and boggy.

**Lymphatic System.** There was no general glandular enlargement. A few discrete, shotty nodes were felt in both cervical triangles and there were several small glands in the right axilla. The abdominal lymph nodes and those at the hilum of each lung were small, pale and on section appeared quite cellular. There was one large gland at the hilus of the liver; on section this gland showed a grayish, cellular, surface with numerous small petechiæ. Retroperitoneal and pelvic glands did not appear grossly abnormal.

**Heart.** There were numerous small, subepicardial hemorrhages. The endocardium was dull, with numerous petechiæ. The myocardium was mottled, pinkish-yellow. On the cut surface, the inner two-thirds of the heart wall was yellowish-red, quite dull and opaque, as if extensively necrotic. At one commissure of the pulmonic valve there was a small, grayish vegetation, firmly attached to the vessel wall. There were several mural thrombi over the lower half of the inner surface of the left ventricle; many of these were firmly attached. The coronary arteries were patent throughout.

**Lungs.** The left weighed 800 gm, the right 600; both showed small subpleural hemorrhages with a mottled grayish-blue surface and felt subcrepitant throughout. The cut section was mottled, with many dark red areas. There was extreme congestion and edema.

The *spleen* weighed 150 gm. and was quite firm. The cut surface was grayish-pink, the Malpighian bodies poorly defined.

The *liver* weighed 1425 gm. The capsule was smooth and transparent. The cut surface was mottled, yellowish-brown in color. The portal areas were gray and opaque. No hemorrhages were seen in liver or spleen.

The *kidneys* each weighed 115 gm. and were similar in appearance. The capsule stripped easily, leaving a smooth surface with numerous petechial hemorrhages. The cut surface was pale. The mucosa of the kidney pelvis and of the ureters showed many petechiæ.

**Gastro-intestinal Tract.** There were many small petechiæ in the mucosa of the stomach and intestine and on the serosa of the small and large intestine. The solitary follicles and Peyer's patches were not more conspicuous than normal.

**Pelvic Organs.** The bladder mucosa showed many petechial hemorrhages. The uterus contained a small blood clot. No thrombi were found in the pelvic vessels.

**Bone Marrow.** Marrow from the middle third of the femur was grayish-pink in color and appeared quite cellular, as did the sternal, vertebral and rib marrow.

The *brain* weighed 1300 gm. The meninges were thin and transparent. Small petechial hemorrhages were seen both on the surface and cut surfaces. In some regions there were small areas which appeared somewhat softer than the surrounding tissue.

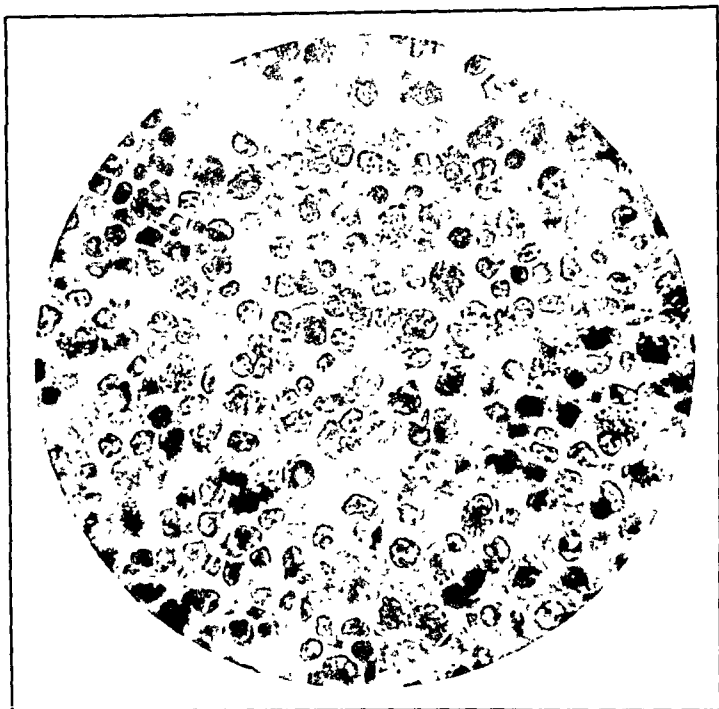


FIG. 1.—Photomicrograph of section of bone marrow from the middle third of the femur. ( $\times 970$ ).

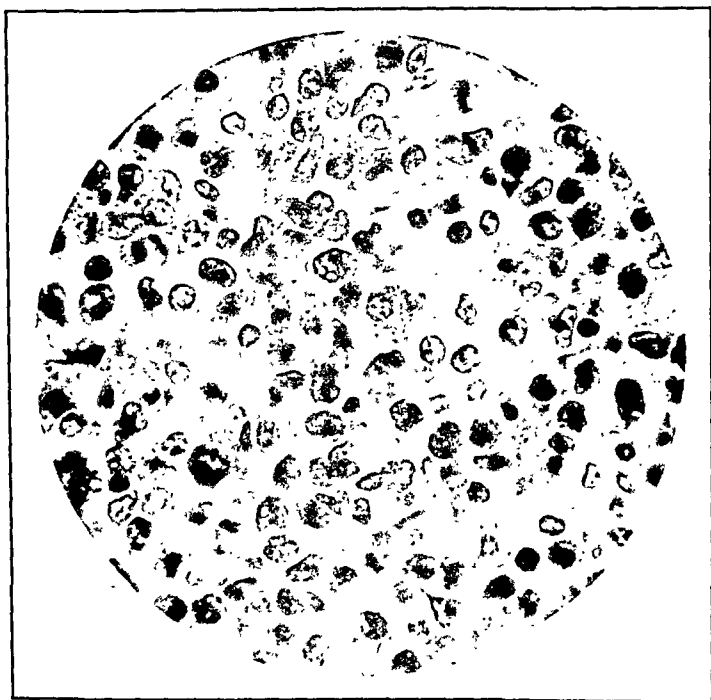


FIG. 2.—Photomicrograph of section of spleen ( $\times 970$ ). In both Fig. 1 and Fig. 2 the cells with granular cytoplasm are eosinophils.



**MICROSCOPIC NOTES.** *Heart.* In the subepicardial fat a few eosinophilic polymorphonuclear cells were seen. The inner half of the ventricular wall showed extreme inflammatory changes. There was partial or complete necrosis of much of the muscle. The necrotic areas were densely infiltrated with cells, most of which were eosinophils. An occasional eosinophilic myelocyte, neutrophilic myelocyte and very rare adult neutrophil could be identified. Many bacteria were seen in the necrotic areas and many of the small vessels contained infected thrombi. There was no evidence of healing. The endocardium was greatly thickened, infiltrated with cells and covered by autemortem blood clot. The outer half of the ventricle showed cloudy swelling only.

*Lungs.* There were small hemorrhages beneath the pleura and marked edema and congestion. Many alveoli were filled with well preserved red blood cells and only a few white blood cells. In some areas the alveoli contained an intensely cellular exudate consisting chiefly of eosinophils. Occasional eosinophilic and neutrophilic myelocytes were seen, with very rare adult neutrophils. There was very little peribronchial infiltration.

*Spleen.* The pulp was densely infiltrated with cells, many of which were eosinophils. Rare myelocytes and neutrophilic polymorphonuclears were scattered in small numbers among the numerous eosinophils and mononuclears. In some areas the infiltration was so dense that there appeared to be necrosis of the splenic pulp. The majority of the mononuclears were similar to those predominating in the bone marrow and occurring in large numbers in the lymph glands and portal spaces of the liver. These cells were obviously early cells, relatively undifferentiated in the hematoxylin and eosin sections. The nuclei were pale and occupied nearly all of the cell area; the cytoplasm was scanty and without granulations. Rare megakaryocytes were seen. The Malpighian bodies were small.

*Liver.* There was a moderate cloudy swelling with a few small areas of hemorrhage. Scattered eosinophils were seen in the sinusoids. The portal spaces showed a moderate infiltration with eosinophils and small, round mononuclears.

*Kidneys.* Occasional isolated hyalinized glomeruli were seen. There were a few small areas of hemorrhage. Between the tubules there were small collections of cells, for the most part eosinophils and small round cells with pale nuclei and very little cytoplasm.

*Uterus.* The musculature appeared normal but scattered eosinophils were seen between the muscle bundles.

*Lymphatic System.* The lymph nodes were very cellular but the normal structure could still be made out. The sinusoids contained many eosinophils and rare neutrophilic myelocytes and polymorphonuclears. There were large numbers of small, pale mononuclears similar to those seen in the spleen, kidneys and portal spaces of the liver. Several of the glands showed areas of hemorrhage. Occasional megakaryocytes were seen in the sinusoids. A few isolated nucleated red blood cells were identified. There was no evidence of fibrosis.

*Bone Marrow.* At the time of autopsy, 2 hours after death, a sample of sternal bone marrow was obtained and emulsified in the patient's serum. The cellular suspension was studied in supravital preparations stained with neutral red and Janus green and in fixed films stained with Wright's stain. Differential count of 1000 cells in the fixed preparation was as follows: neutrophilic myelocytes, 0.2%; eosinophilic myelocytes, 0.9; eosinophils with single lobe nucleus, 0.1; eosinophils with two lobed nucleus, 0.2; blast cells, 98.6. The blast cells presented pale nuclei, which in many instances contained nucleoli; the cytoplasm was moderately to deeply basophilic, without specific granules. No adult neutrophilic cells were seen. Very

rare megaloblasts, erythroblasts and normoblasts were seen but none were encountered in the differential enumeration of 1000 cells. No megakaryocytes were seen in either the fixed or supravital preparations. With the supravital stains the predominant cell was a rather small, mononuclear cell, the cytoplasm of which contained many mitochondria; a few of these cells contained one or two fine neutral red granules. It was thought that the majority of these cells were myeloblasts or "A" myelocytes (Sabin).

Sections from the marrow of the middle third of the femur, rib, vertebra, and sternum (hematoxylin and eosin and Giemsa) appeared very cellular, with the marrow spaces packed with small mononuclear cells similar to those described in the spleen, lymph glands, kidneys and portal spaces of the liver. Immature eosinophils were very conspicuous and numerous. In some areas eosinophilic myelocytes were so abundant that they completely dominated the picture. In other areas they were less prominent but always present in large numbers. Only occasional neutrophilic myelocytes and nucleated red blood cells were found. A few scattered megakaryocytes were seen.

*Brain.* The meninges were somewhat thickened and infiltrated with cells, many of which were eosinophils. Many of the small vessels in the meninges and in the brain substance contained thrombi. Small areas of hemorrhage into the brain substance were seen and there were several small areas of encephalomalacia.

*Anatomical Diagnosis.* Acute leukemia, with infiltration of bone marrow, spleen, lymph glands, liver and kidneys. Bronchopneumonia. Acute myocarditis with necrosis. Mural endocarditis. Thrombi in small radicals of cerebral vessels with focal areas of hemorrhage and encephalomalacia. Hemorrhages into skin, mucous membranes and viscera.

The clinical and pathologic observations establish the diagnosis of leukemia. The short duration of the illness, the presence of numerous very immature cells in the peripheral blood and tissue infiltrations, the terminal purpura and necrotizing infections are characteristic of the acute form of the disease. In view of the great predominance of eosinophils in the blood and tissues, the term "acute eosinophilic leukemia" is useful in differentiating this from other types of myelogenous leukemia. There was no clinical or pathologic evidence of trichiniasis, Hodgkin's disease or other condition which might have contributed to the striking eosinophilia.

*Discussion.* Previously recorded cases of acute eosinophilic leukemia conform to the above description of the disease except for minor details. (Schmidt-Weyland<sup>1</sup>, Hay and Evans<sup>2</sup> and McCowan and Parker<sup>3</sup>).

Our case differs from these 3 chiefly in the longer duration, the presence of many myeloblasts in the peripheral blood, in the severity of the hemorrhagic phenomena and in the occurrence of terminal, agranulocytic inflammatory changes.

Acute leukemia is usually characterized by the extreme immaturity of the type cell in the peripheral blood and in the tissue infiltrations. In all 4 recorded instances of acute eosinophilic leukemia, however, the predominant cell in the peripheral circulation has been the adult eosinophil, with smaller numbers of cells of varying degrees of immaturity. Pantou, in his discussion of the paper of

McCowan and Parker,<sup>3</sup> doubts the diagnosis of acute leukemia in such patients because of the predominance of mature forms in the peripheral blood. In spite of this unusual finding, the characteristic changes in the various organs have been those of undoubted leukemia in the 3 cases in which satisfactory autopsy material has been available for study. Hay and Evans observed that practically all of the eosinophils in the spleen and lymph nodes were mature forms, with very few eosinophilic myelocytes. They concluded that there was no histologic evidence of local production of eosinophils in any of the organs except the bone marrow. To investigate this point further, differential counts of the eosinophils were made by us in the fixed sections of various tissues of the patient here recorded. In appropriate sections, examined under the oil-immersion objective, the larger, non-lobulated, rather light staining nucleus of the myelocyte could be accurately differentiated from the smaller, lobulated, darker nucleus of the adult eosinophil. These differential counts (Table 1) show a proportion of myelocytes to adult eosinophils significantly higher in the bone marrow, spleen, lymph nodes and portal spaces of the liver than in other tissues. In these areas there were also large numbers of immature mononuclear cells with pale nuclei, similar to the predominant cells in the bone marrow thought to be very early myelocytes or myeloblasts on the basis of their supravital staining reactions. It seems reasonable to conclude from this evidence that the above mentioned areas were participating in the active production of eosinophils.

TABLE 1.

Tissue.	Eosinophilic myelocytes (per cent).	Adult eosinophils (per cent).
Bone marrow (femur) . . . . .	96.5	3.5
Spleen . . . . .	17.5	82.5
Abdominal lymph gland . . . . .	28.5	71.5
Liver (portal spaces) . . . . .	24.0	76.0
Liver (sinusoids) . . . . .	7.0	93.0
Lung (bronchopneumonia) . . . . .	3.5	96.5
Heart (necrotizing myocarditis) . . . . .	4.5	95.5
Infected mural thrombus . . . . .	5.5	94.5

It is of interest that the exudate in the areas of inflammation was composed almost entirely of adult eosinophils. Numerous lymphoid and other mononuclear cells were present but adult neutrophils were exceedingly rare. There was widespread necrosis and very little evidence of healing. The changes in the inflammatory areas suggested those seen in agranulocytosis except for the presence of large numbers of eosinophils. The striking lack of neutrophils in the peripheral blood and tissues is easily understood; neutrophilic myelocytes were extremely rare in the bone marrow and there was no evidence of any significant extramedullary neutrophilic myelopoiesis. These observations are in accord with those of Jaffe,<sup>4</sup> who has shown that the inflammatory defense response in

leukemia depends on the presence of myeloid tissue able to produce a sufficient number of mature neutrophils. Apparently the eosinophil is unable to assume the responsibilities of the neutrophil in the inflammatory defense reactions of the body.

**Summary.** A patient with acute eosinophilic leukemia is described. The clinical and pathologic features of the disease are similar to those observed in other types of acute leukemia, except for the type and maturity of the affected cell group. Evidence of extramedullary production of eosinophils is presented. Lack of adequate neutrophilic myelopoiesis was reflected in the scarcity of neutrophilic granulocytes in the necrotizing inflammatory exudates, which were composed chiefly of adult eosinophils.

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### A QUANTITATIVE STUDY OF RENAL INJURY IN A CASE OF ACUTE POISONING BY BICHLORID OF MERCURY WITH A NOTE REGARDING TREATMENT.

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Numerous articles have appeared dealing with various aspects of acute mercury poisoning, both experimental and clinical. However, a careful study of the renal injury by means of recently improved kidney function tests, and as reflected by the quantitative study of abnormal aspects of the urine, is conspicuously lacking. It therefore seems timely to report such a study, made of a case of acute poisoning by mercuric chlorid, recently observed in our University Hospital.

**Case Report.** At about 4.30 A.M. on December 18, 1933, Mrs. B. V., aged 20, in an attempt to commit suicide swallowed half a glass of water into which were stirred "10 to 15 tablets" of mercuric chlorid. Each tablet contained 0.12 gm. of the salt. The total dose therefore was approximately 1.5 gm. About 10 minutes after ingestion of the poison, she vomited. Five minutes later she was caused to drink 3 pints of milk containing the whites of 5 eggs. Frequent emesis followed. She was admitted to the hospital 1½ hours after ingesting the poison, complaining of weakness, burning sensation in the mouth and pharynx, and epigastric pain.

On admission the patient was rational, oriented and coöperative. She

did not appear to be suffering. She was slightly pale. The pupils were equal, moderately dilated, and reacted normally to light and in accommodation. The ocular fundi were normal. The tongue and throat were red. Examination of the neck was negative. The lungs were clear. The heart was of normal size. Cardiac rhythm was regular. There were no murmurs. The pulse rate was 90. The blood pressure was 94/70. There was slight tenderness in the epigastrium and right upper quadrant of the abdomen. The extremities appeared normal. The tendon reflexes were normal.

The blood Kahn reaction was negative. The hemoglobin was 96% (Sahli). The red blood cell count was 5.33 million; leukocytes, 25,000 per c.mm., with 95% neutrophils. The red blood cells and platelets were normal.

On admission the patient's stomach was washed with a 5% solution of sodium bicarbonate. She was given 30 gm. of magnesium sulphate. The colon was irrigated. Several eggs were ingested during the first few hours in the hospital. Because the patient was unable to retain ingested food and fluids, the administration of intravenous fluids was begun on the morning of admission. On the first, second and third days, when vomiting was most profuse, both physiologic sodium chlorid, and 5% glucose solutions were given. Subsequently, 5% glucose alone was used. An average of 5000 cc. of fluid were given intravenously daily for 22 days. Each of the first 4 days the patient received 1 gm. of sodium thiosulphate and 3 gm. of sodium bicarbonate intravenously. Bowel movements were initiated by means of a tap water enema daily for 15 days.

The patient became progressively more ill during the first 5 days. Weakness was marked. Nausea and vomiting were particularly troublesome. During the first 5 days the vomitus was bloody. Diarrhea did not occur. On the fourth day, slight uterine bleeding began. (She had an abortion 10 weeks prior to admission, and since that time had had irregular uterine bleeding.)

On the fifth day the patient was very ill. Throughout most of the day she was semicomatose. On the following day the patient became oriented and fully conscious; however, she remained critically ill. Anorexia, nausea, gastric distress and vomiting continued to be the predominant features of her illness. Attempts to eat and drink were followed by vomiting.

Her condition did not change essentially until the 14th day when she complained less of nausea, and seemed brighter and more responsive. From this time on there was progressive improvement. About the 17th day she began retaining sips of water and small amounts of liquid nourishment. Her ability to retain ingested food and fluid gradually increased, but not sufficiently to permit the stopping of intravenous fluid until the 23d day. She was then given abundant fluids orally, and a soft diet containing about 50 gm. of protein daily. Improvement continued and the patient was discharged from the hospital on January 15, 1934. She was advised to continue restriction of activity, copious intake of fluid and the soft diet with restricted protein.

Frequent visits as an out-patient allowed us to follow her subsequent course, until we considered complete cure had resulted, 3½ months after the poisoning.

**Renal Studies.** Throughout the illness quantitative studies of the kidney injury were made. Renal function was measured by the urea clearance method of Van Slyke,<sup>1</sup> by concentration test according to the improved technique of Lashmet and Newburgh,<sup>2</sup> and by phenolsulphonaphthalein excretion. Proteinuria was measured



by the Lashmet-Newburgh method.<sup>3</sup> Formed elements in the urine were counted after the manner described by Addis.<sup>4</sup> Frequent determinations of the non-protein nitrogen in the blood were made.

The urinary abnormalities and blood findings appear in Table 1. The results of the renal function studies, together with some of the other more important data, are presented graphically in Fig. 1.

TABLE 1.—URINE AND BLOOD FINDINGS.

Date.	Volume, cc.	Reaction to litmus.	Protein, gm. per 24 hrs.	Urine findings.				Blood findings.				
				Formed elements excreted per 12 hours.*				Hemoglobin, %.	Red blood cells, millions per c.mm.	White blood cells, per c.mm.	Non-protein nitrogen, mg. %.	Carbon-dioxid combining power, vol. %.
				Casts.	Renal epithelial cells.	Leukocytes.	Erythrocytes.					
Dec. 18	1700	Acid	8.5	Many hyalin	90,000,000	Few	Few	96	5.33	25,000	45.1	
19	2400	Acid	22.0	and granular 185,000 hyal. and gr.	144,000,000	Few	2,232,000†	..	....	...	45.1	
20	4400	Alk.	12.0	....	489,000,000	Few	3,720,000	..	....	...	45.1	
21	3900	Alk.	3.7	....	318,000,000	1,344,000	17,550,000†	..	....	...	46.9	
22	4800	Neut.	2.45	298,900 hyalin 672,000	51,319,000	1,344,000	895,000	..	....	12,200	39.7	45.1
23	3800	Neut.	....	....	27,580,000	1,515,960	2,122,344	..	....	...	53.1	
24	3630	..	1.24	....	....	....	....	..	....	...	57.0	
25	3600	..	0.72	....	....	....	....	..	....	...	57.0	
26	2180	..	0.56	....	....	....	....	..	....	...	57.0	
27	5090	..	....	....	....	....	....	88	5.8	11,200	57.0	
28	3280	..	0.57	....	....	....	....	..	....	...	57.0	
29	4850	..	0.66	....	....	....	....	..	....	...	57.0	
30	5050	..	0.55	....	....	....	....	..	....	...	57.0	
31	3150	..	0.99	....	....	....	....	..	....	...	57.0	
Jan. 1	4000	..	0.60	....	....	....	....	..	....	...	57.0	
2	5580	..	0.60	....	....	....	....	..	....	...	57.0	
3	3700	Acid	....	230,000	1,500,000	Few	2,500,000	..	....	...	32.9	
4	4570	..	....	....	....	....	....	..	....	...	32.6	
5	4000	..	2.5†	....	....	....	Grossblood†	..	....	...	32.6	
6	3460	..	....	....	....	....	....	..	....	...	32.6	
7	3420	..	....	....	....	....	....	..	....	...	32.6	
8	4700	..	1.7†	....	....	....	....	..	....	...	32.6	
9	2250	..	0.42	....	....	....	....	..	....	...	32.6	
10	2300	..	0.36	....	....	....	....	..	....	...	32.6	
11	1550	..	....	....	....	....	....	..	....	...	32.6	
12	1700	..	0.40	....	....	....	....	67	....	...	32.6	
13	2020	..	0.30	....	....	....	....	69	....	...	32.6	
14	2700	..	Trace	....	....	....	....	..	....	...	32.6	
27	..	Acid	Faint trace	35,064 hyal. and gr.	657,000	11,000,000	2,235,000	..	....	...	32.6	
Feb. 7	..	Acid	0	0	0	Few	0	..	....	...	32.6	
28	..	Acid	0	0	0	Few	0	..	....	...	32.6	
Apr. 5	..	Acid	0	0	0	8,605,000	210,000	85	4.8	8,900	32.6	

\* At times urine collected for urea clearance tests was used for counting formed elements in the sediment. These counts were converted to values per 12 hours.

† Urine obtained by catheter.

‡ Uterine bleeding occurred on these days.

Gross urinary abnormalities existed during the first few days. Proteinuria was great during the first 3 days, the maximum amount of protein (22 gm.) being excreted on the second day. It gradually diminished after the third day, although it persisted for more than 6 weeks. Sporadic increases are noted at times when uterine bleeding occurred.

Cylindruria was also great during the first few days. The maximum was recorded on the sixth day. When the urine was alkaline cast counts were not attempted. Casts were found as long as there was proteinuria.

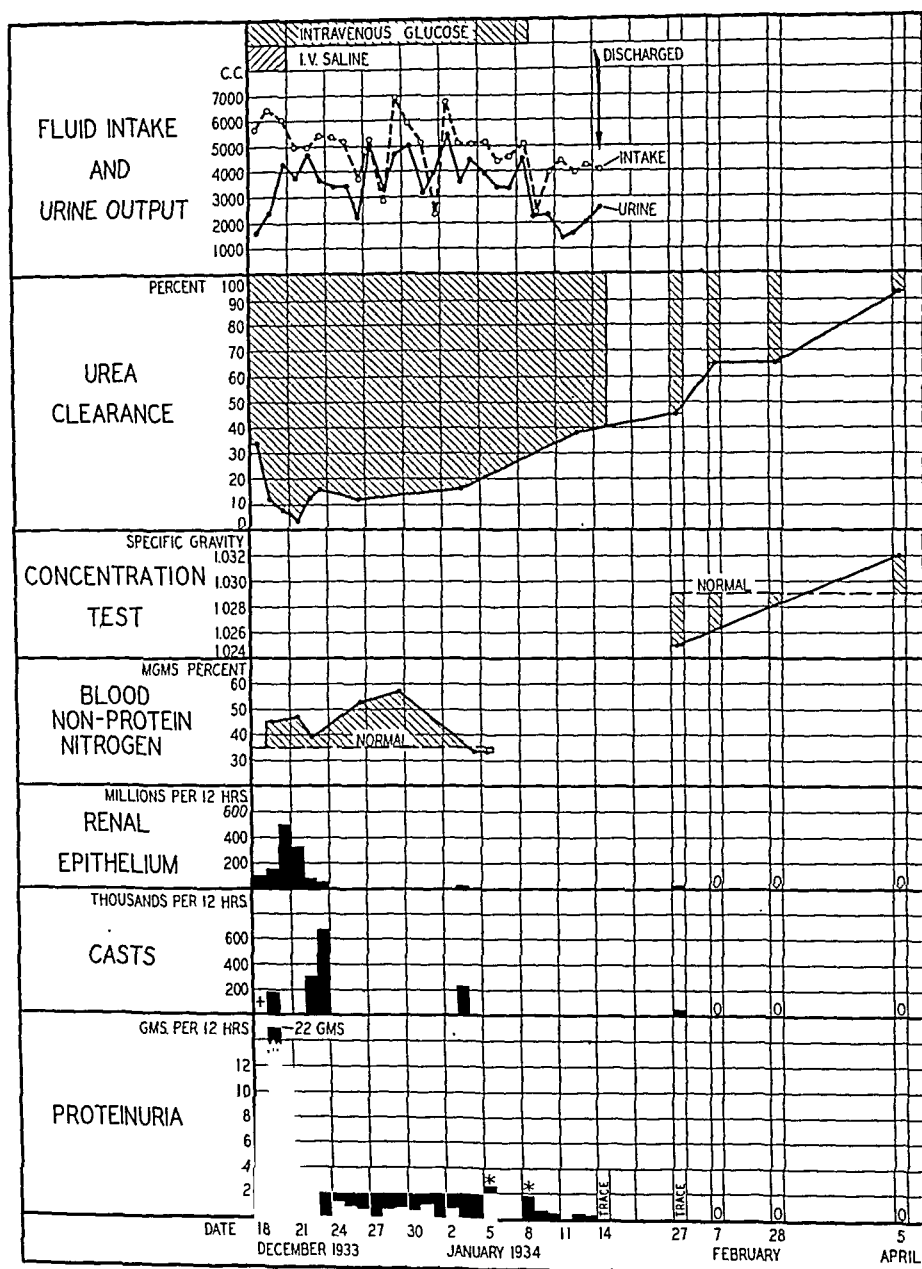


FIG. 1.

\* Bloody urine (uterine bleeding).

The most remarkable abnormal finding in the urine was the excretion of huge numbers of renal epithelial cells during the first few days. These cells were excreted in increasing numbers until the third day, when the maximum of 489,000,000 were found in a 12-hour period. There was a rapid decrease in the excretion of renal epithelium after the third day, although these cells were seen in small numbers as long as proteinuria was observed.

The number of leukocytes seen in the urine was never strikingly abnormal.

Evaluation of the erythrocytes observed in the urine is difficult due to the fact that uterine bleeding occurred at times. However, the urine obtained by catheter on the second day contained slightly more red blood cells than was observed in normal individuals by Addis.<sup>5</sup>

The renal function studies, and especially the results of the frequent urea clearance tests, are most instructive.\* The urea clearance test shown on the graph for the first day was done 6 hours after the patient was admitted ( $7\frac{1}{2}$  hours after taking the poison). This early kidney function was only 34% of normal. The function continued to fall until it reached the low value of 5% of normal on the fourth day, after which it remained between 10% and 17% for 2 weeks. Throughout this time the blood non-protein nitrogen rose only slightly, the highest value (on the twelfth day) being 57 mg. per 100 cc. of blood. There was a gradual increase in the urea clearance during the third and fourth week, but by the time the patient was discharged from the hospital it had risen to only 39% of normal.

On the patient's first return visit, January 27, she felt much improved. Urea clearance was 46% of normal. On this date a concentration test was done. It showed impairment of renal func-

\* In doing the urea clearance tests, the method used to determine the urea content of blood and urine requires the digestion of urea by the enzyme urease. It is known that mercury, if present in a sufficient quantity, interferes with the activity of urease. Since mercury is excreted in the urine of patients poisoned with bichlorid of mercury, it was necessary to determine whether the sample of urine used in performing these tests contained enough mercury to interfere with the urease digestion. Accordingly, urease digestions were carried out on standard solutions of urea, to which different amounts of mercuric chlorid were added.

Following are the results:

Added HgCl <sub>2</sub> , mg.	Added mercury, mg.	Digestion, %.
0.02 . . . . .	0.0148	100
0.03 . . . . .	0.0222	96
0.04 . . . . .	0.0295	87
0.06 . . . . .	0.0443	81
0.10 . . . . .	0.0739	50

These findings show that there is no appreciable interference with urease activity unless 0.03 mg. of mercury is present. Considering the large volume of urine excreted by this patient each day, it is unreasonable to believe that the concentration of mercury in the urine was sufficiently great to interfere with the activity of urease.

tion. The maximum specific gravity was 1.025. Normally, by the technique used, it is 1.029 or above. Excretion of 6 mg. of intravenously injected phenolsulphonaphthalein was as follows: 30 minutes after injection, 40% return of dye; 60 minutes, 10%; 120 minutes, 10%; a total of 60%. On February 7, for the first time, the urine showed no abnormality. The urea clearance, however, remained below normal, being only 66%. On February 28, the same urea clearance value was observed. On this day the patient complained that her hands felt swollen. No edema was observed. Blood serum showed the following protein content: Total protein, 7.2 gm. per 100 cc.; albumin, 4.75 gm.; globulin, 2.45 gm. The albumin/globulin ratio was 1.9.

The patient was not seen again until April 5, 1934. On this date she returned feeling entirely well. She had gained 5 pounds in weight. Increasing activity had been attended by no symptoms. Physical examination was negative. Urinalysis showed no abnormality. Urea clearance was 92%. Concentration test showed normal ability to concentrate the urine, the maximum specific gravity being 1.032. Excretion of 6 mg. of intravenously injected phenolsulphonaphthalein was also normal: 30 minutes after injection, 50% return of dye; 60 minutes, 15%; 120 minutes, 10%; a total of 75%. Since there was no evidence of renal damage, the patient was considered completely cured.

**Discussion.** The most interesting aspect of this case is the course of the renal changes. Within a few hours after ingestion of the nephrotoxic substance, marked renal damage existed as shown by gross proteinuria, cylindruria, the excretion of large numbers of renal epithelial cells, and serious impairment of kidney function. Seven and a half hours after the poisoning the urea clearance was only 34% of normal, and the very low level of 5% of normal was reached on the fourth day. The renal function remained at a strikingly low level for 2 weeks, after which continued improvement occurred. In contrast to the rapid decrease, improvement of kidney function was relatively slow, and normal function was not noted until  $3\frac{1}{2}$  months after the poisoning.

It should be noted that impairment of function existed several weeks after the urine ceased to show any abnormality. On each occasion when simultaneous renal function tests were done, there was good agreement between the results of the concentration test and the urea clearance test.

Of particular interest is the fact that during the time when there was marked kidney damage as shown by the low urea clearance values, and throughout which time vomiting was profuse, the non-protein nitrogenous wastes in the blood were never found to be higher than 57 mg. %. This we feel is due to a provision for a

high fluid intake *from the outset*, thus allowing sufficient solvent for excretion of the waste products.

At this point a brief consideration of the treatment of acute mercurial poisoning is *apropos*. Therapy for this type of poisoning can be divided into four main headings: (1) measures to prevent absorption and rid the patient of the unabsorbed poison; (2) treatment of shock, if it occurs; (3) measures to detoxify the absorbed mercury; and (4) measures to correct, or compensate for, functional disturbances resulting from the poison.

There can be no doubt about the importance of preventing the absorption of the poison, and of causing its rapid evacuation. The methods to be used are too well known to warrant further comment here. The suggestion made by Mintz<sup>6</sup> that, as a prophylactic measure, tablets of mercury bichlorid be coated with an emetic such as copper sulphate, seems wise.

Antishock treatment is amply discussed elsewhere, and will not be dealt with in this paper.

McBride and Dennie<sup>7,8</sup> have advised the intravenous use of sodium thiosulphate, claiming that detoxication resulted in the body. However, the animal experiments of Haskell, Henderson and Hamilton,<sup>9</sup> Melville and Bruger,<sup>10</sup> Young and Taylor<sup>11</sup> and others, show unquestionably that this medication is of no clinical value. To date no successful antidote for absorbed mercury has been demonstrated.

Measures to be taken to combat the abnormal physiology resulting from damage caused by the poison, deserve more consideration. The pathology of greatest clinical importance is, in most cases, the kidney damage. That this is rapid in development and causes marked impairment of the function of these organs is well illustrated by this case.

It has been demonstrated by one of us (F. H. L.)<sup>12</sup> that the damaged kidney needs much more fluid with which to excrete waste products. The amount needed depends upon the extent of the kidney damage. If sufficient fluid is provided, *even in the presence of marked renal damage*, there is satisfactory excretion of wastes, and retention does not occur.

The choice of fluid to be administered is important. In most cases of mercury bichlorid poisoning, profuse vomiting occurs. In this way much of the body chlorid may be lost. Peters, Eisenman and Kydd<sup>13</sup> have recently shown that the circulating chlorids are diminished in most cases of acute mercurial poisoning. They advise the administration of a large volume of a physiologic solution of sodium chlorid in order to restore normal concentration of chlorid in the body fluids.

*Excessive* amounts of sodium salts, however, we feel should not be given since storage of sodium will increase the tendency to edema that is prone to occur in cases of severe poisoning with mercury.

Reason for guarding against edema lies in the fact that the kidneys will share in any generalized edema, and edema of the kidneys would further impair the function of these organs. Consequently, when it is desirable to administer abundant fluid intravenously, we believe physiologic saline solution should be used only when a definite need of chlorid exists. In all other circumstances we prefer to use a 5% solution of glucose. The glucose is burned, furnishing a small supply of energy, and preventing the occurrence of ketosis.

That 5% glucose can be administered intravenously in large amounts daily for a long time with no harmful results is shown by this case. On each of the first 3 days, when vomiting was most profuse, 2 liters of physiologic saline were given intravenously, followed by 3 liters of a 5% solution of glucose. After the third day, 5% glucose alone was administered. An average of 5000 cc. were given daily through the twenty-second day. Thus an average output of over 3700 cc. of urine occurred daily. It is to be noted that in the presence of marked renal damage there was no difficulty in eliminating this large volume of urine and that edema at no time was present.

**Conclusions.** 1. A quantitative study of the renal injury in a case of acute poisoning with bichlorid of mercury is reported.

2. It is shown that extensive renal damage accounting for marked impairment of function occurred almost immediately, and existed for several weeks, after which there was progressive but relatively slow improvement until normal function returned  $3\frac{1}{2}$  months after the poisoning. Impairment of renal function continued for weeks after all urinary abnormalities had disappeared.

3. The treatment of acute mercury poisoning is briefly discussed. The importance of the administration of a large amount of fluids *from the very outset*, to compensate for the impairment of renal function, is pointed out. Indications for the use of physiologic solutions of saline and of glucose are discussed.

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## ACUTE POTASSIUM BICHROMATE POISONING.

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CHRONIC chromium poisoning is met with not infrequently in industry, but acute potassium bichromate poisoning from a single large dose taken by mouth is relatively uncommon, 69 cases having been reported. Reischer and Glesinger<sup>1</sup> in reporting a case made a comprehensive survey of 63 cases which they found in the literature. They overlooked a case reported by Philipson.<sup>2</sup> Jonsson,<sup>3</sup> Bernard,<sup>4</sup> and Biancalani<sup>5</sup> have reported 4 cases since 1922.

TABLE 1.—URINARY FINDINGS.

	Urine.	Alb.	Urinary findings.			
			Sp. gr.	N. P. N. mg.	Creatin- in 100 cc.	Icteric index.
Feb. 25	Acetone	++				
27	Acetone	+				
Mar. 1	Oliguria Few R. B. C. and W. B. C.	+	1012	150	6.75	
2	Oliguria Few R. B. C. and W. B. C.	+	1010			
3	Oliguria Few R. B. C. and W. B. C.	+	1010			9
4	Oliguria Few hyalin and granular casts Few R. B. C.	+++	1012	205	8	
6	Oliguria Few R. B. C.	++	1010	200	7.5	
8	Sediment—neg. Urine output normal	+	1012	150	5	
10	Few W. B. C. (uncatheterized specimen)	++	1010	90	3.75	
13	Same			47.5	1.9	9
15	Same			43	1.5	
17	Same			30	1.3	
22	Same			26	1.2	8
29	Same			26	1.15	
June 28	Amber—cloudy Acid  Micro, few R. B. C. Loaded c. epith. cells and bacteria	ft. tr. Feels fine,	1018 gained	27 30 lbs.)	Cholesterol 174 Cholesterol 84 esters  B. P. 140/100	

The following case, the first to appear in the literature of this country, is illustrative of those previously described.

**Case Report.** Patient I. O., aged 25, was admitted to the hospital on February 25, 1933, complaining of dizziness, intense thirst, vague abdominal pains, and vomiting of greenish-yellow fluid which was sometimes blood streaked. Her illness began on February 23, with a paroxysm of vomiting. No other symptoms were elicited. The family and past histories were unimportant.



FIG. 1.—Toxic rash.

Physical examination revealed a thin, white female, not acutely ill. The skin was dry and inelastic. There were no other positive findings. The rectal temperature was  $100^{\circ}$ , pulse 90, respirations 24, and blood pressure 90/60. The urine showed only 2+ acetone. The patient was neurotic, very uncoöperative, and refused the routine blood chemistry.

Two days after admission, she complained of a dull pain in the epigastrium and right upper quadrant, which were tender and rigid. The next day, the temperature rose to  $101^{\circ}$ , the pain, tenderness and rigidity became more severe and the liver edge was felt 1 inch below the costal margin. There was no jaundice, but she continued to vomit once or twice a day.



During the next 4 days, the signs and symptoms referable to the liver disappeared and the temperature became normal.

Four days after admission, she became more coöperative, and the following laboratory reports were obtained. The blood Wassermann and Kahn tests were negative, the blood count showed 15,000 leukocytes with 87% polymorphonuclear leukocytes and 13% lymphocytes; the red blood cell count was 4,300,000 and the hemoglobin 85% (Sahli); the blood non-protein was 150 and the blood creatinin 6.75 mg. 100 cc. The 24-hour urine output was 600 cc.; the specific gravity was 1.012, there was a trace of albumin, a few R. B. C. and W. B. C. With these findings of severe nephritis preceded by severe hepatitis, the patient was closely questioned but denied having taken any medication before admission. A urine analysis was negative for mercury.

On March 4, the blood non-protein nitrogen had risen to 205 and the creatinin to 8. There was still an oliguria and the urinary findings continued to indicate renal damage. The feces contained occult blood. At this time, the patient did not seem very ill except for the marked dehydration which persisted in spite of a large fluid intake. On this day, an erythematous, pin-point, macular rash appeared on the arms and legs. It faded on pressure, and did not itch. It spread rapidly and became confluent. The attending dermatologist diagnosed it as a non-specific toxic rash. It began to fade on March 8 and disappeared on March 13.

On March 5, the patient admitted that on February 23d, she had swallowed a heaping teaspoonful of orange-yellow crystals dissolved in water. The original bottle was obtained, and found to contain potassium bichromate crystals. The urine, repeatedly analyzed for chromium, was reported positive by Dr. P. A. Riedal, the hospital pathological chemist. This was verified by Dr. A. C. Gettler, the New York City toxicologist.

The blood non-protein nitrogen and creatinin reached normal on March 17. After the initial oliguria, the urine volume rose rapidly to normal, but the specific gravity remained low throughout, and there remained a trace of albumin and a few W. B. C. in uncatheterized specimens. The vomiting ceased on March 12. Fishberg concentration tests were done frequently and showed a low fixed specific gravity ranging between 1.008 and 1.012; an isolated reading of 1.022 was obtained near the end of her hospital stay. Two urea clearance tests (March 22-29) showed 80% of normal function. The serum albumin was 2.6% and the serum globulin was 1.3% on March 6. The cholesterol was 160 on March 22. The blood pressure remained low throughout, averaging about 100/70. The temperature, pulse rate, and respiratory rate remained normal except for a temperature of 101° on February 28. Roentgenograms of the heart, lungs, and abdomen were normal. A blood count (March 28) showed 8100 leukocytes, 81% polymorphonuclear leukocytes and 19% lymphocytes; the red blood cell count was 3,900,000 and the hemoglobin 70% (Sahli).

The patient was discharged on April 2, in good health. She was seen again on June 28. She was enjoying excellent health and had gained 30 pounds. Her blood pressure was 140/100; her N. P. N. was 27; her urine showed a specific gravity of 1.018, and was essentially normal.

The treatment was entirely symptomatic. Fluids were administered by mouth, hypodermoclysis and proctolysis. High hot colonic irrigations were given when the diagnosis was made.

**Summary.** 1. A case of acute potassium bichromate poisoning with recovery is reported. There are no other reports in the literature of the United States.

2. The features of this case are the presence of an enlarged tender

liver, a skin eruption and the finding of chromium in the urine. Previous case reports fail to mention such findings.

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## THE CLINICAL APPLICATION OF DUODENAL EXTRACT (MACALLUM-LAUGHTON) IN DIABETES MELLITUS.

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THE possibility that an agent is produced in the duodenal mucosa when food is ingested, which activates the internal secretion of the pancreas, as secretin liberates the external secretion, was considered, in 1906, by Moore *et al.*<sup>1</sup> These investigators claimed benefit from secretin—perhaps unpurified—in the treatment of 3 diabetics but their findings were not confirmed. In 1 of the cases the results seemed conclusive.

Ivy and Fisher,<sup>2</sup> in 1924, isolated an insulin-like substance from the mucosa of the stomach and duodenum, and Dixon and Wadia,<sup>3</sup> in 1926, obtained an insulin-like action with duodenal extracts given to dogs subcutaneously.

Macallum,<sup>4</sup> in 1929, stated that, in his belief, there was an insular hormone produced in the duodenum when sugar entered the intestine. Heller,<sup>5</sup> in 1929, found a lower induced hyperglycemia after giving an extract of the duodenal mucosa to rabbits and dogs than when none was administered.

In 1930, Laughton and Macallum<sup>6</sup> reported that a duodenal extract, prepared by them, influenced the curve of an induced hyperglycemia in the normal but not in the depancreatized animal.

Laughton *et al.*,<sup>7</sup> in 1931, stated that clinical results appeared to parallel those obtained on animals. The beneficial effects were confined to the mild diabetic not requiring insulin. There were no case reports.

In 1932, Laughton and Macallum<sup>8</sup> reported, in detail, the effect of a duodenal extract on dogs and rabbits. This preparation is the one used in the present clinical study. The extract, obtained by acid extraction from beef mucosa, had no effect on the normal blood sugar of rabbits, but it moderated the hyperglycemia artificially induced by giving glucose intravenously and when epinephrin was given. This effect lasted, after a period of 7 to 10 days' administration, for about 2 weeks. There was no effect on the normal blood sugar or in the totally depancreatized dog, but the partially depancreatized dog was benefited by subcutaneous and oral administration of the extract. It was proved that the extract did not contain secretin or insulin.

La Barre,<sup>9</sup> in 1932, obtained by acid and alcoholic extractions from the duodenal mucosa a substance which he called incretin. Given intravenously, orally or subcutaneously to rabbits and dogs, it produced hypoglycemic convulsions and in some instances death. Unlike the Macallum-Laughton preparation, incretin lowered the blood sugar of the normal dog but it too had no effect on the blood sugar of totally depancreatized animals.

In the fall of 1932, our study with the Macallum-Laughton extract on human diabetics was begun.

The behavior of the blood sugar and its responses to diet and insulin are so variable in the diabetic that conservatism must attend any conclusions. We must remember that improvement may ensue with changes in diet alone. This factor has undoubtedly influenced our results, though we believe we have in all fairness planned this study in such a way as to assess fairly the activity of the remedy employed.

**Methods.** Increases in carbohydrate and total calories to the limit of tolerance before, and further increases after beginning the extract have been made to observe changes in tolerance.

In mild diabetics, with a relatively high tolerance for carbohydrate and total calories, glucose tolerance tests were employed. The curves obtained were used as a measure of improvement. In these tests 100 gm. of glucose were given in 250 cc. of water and blood and urine specimens were obtained before the glucose was given and at intervals of  $\frac{1}{2}$ , 1, 2 and 3 hours after. These tests were made before, during and at varying intervals after extract treatment.

The free use of tolerance tests in this study must not be interpreted as a usual or common practice in the routine management of our diabetics. Aside from this investigation we avoid glucose tolerance tests in all diabetics except where no other test establishes the diagnosis. Furthermore, we have used the tests only when better methods of proof were not applicable.

The effect of the abrupt withdrawal of large doses of insulin before and after the use of duodenal extract has been observed and the approximate period of apparent effectiveness has been roughly estimated by observing

laboratory data over long periods. Subsequent increases in the carbohydrate and total calories were made to find the limit of tolerance.

The blood sugar estimations were done by the new Benedict method,<sup>10</sup> in the Jefferson and Pennsylvania Hospitals, until May 1, 1934, when the old Benedict method was resumed at the Pennsylvania Hospital.

The patients were hospitalized throughout the study except when otherwise specified.

While Macallum and Laughton have administered the extract subcutaneously to animals, we have given it by mouth only. At first we gave 1 gm.  $\frac{1}{2}$  hour before each meal, but as little effect was obtained in the first 2 or 3 days of treatment it seemed that administration in direct relationship to meals was unimportant. Larger doses, up to 6 gm. t.i.d., did not increase the effect. In fact 0.25 gm. given t.i.d. was suitable and we suspect that smaller doses are effective.

Short courses of treatment, 1 week in each month, were tried when the apparent effect was carried over from days to weeks after withdrawal of the extract.

**Illustrative Cases.** CASE 1.—T. G. (Penn. Hosp. No. 17176), male, colored, aged 16, was admitted on July 9, 1934, complaining of increasing drowsiness, loss of appetite, strength and weight with an unquenchable thirst and polyuria of 4 weeks' duration.

**Family History.** One sister had glycosuria, otherwise unimportant. Past illnesses comprised of measles in childhood and he was thought to have a mild hypopituitarism (dystrophia adiposa genitalia) in 1930. At that time glycosuria, which cleared up promptly, was found.

**Present Illness.** Four weeks before admission he lost all desire for cigarettes and at the same time weakness, thirst, polyuria, dryness of the skin, constipation and anorexia became noticeable. These symptoms increased in severity until admission. In the month preceding his admission he lost in weight from 82 to 71 kg.

**Physical Examination.** Pronounced drowsiness, dry skin, nutrition good, intraocular tension normal to digital pressure and infected tonsils. The heart, lungs, abdomen, genitalia and reflexes were normal; the blood pressure was 120/80; height, 71½ in.

**Laboratory Data.** Heavy glycosuria with strong reactions for acetone and di-acetic acid in the urine. The blood sugar was 0.263%, with a severe grade of lipemia and a strong positive reaction for acetone and di-acetic acid in the blood plasma (Rothera-Wishart test). Additional data are included in Table 1.

TABLE 1.—DATA IN STUDY OF CASE 1.

Date, 1934.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.	Wt., kg.
	P.	F.	C.	Cal.					
7/9-7/12	85	47	160	1400	44-104	None	263-67	42.6-50.2	68
7/13-7/22	85	55	140	1400	70-106	None	183-100	30.8-4.2	71
7/23-7/30	85	22	140	1100	100-109	None	103-131	3.4-11.9	75
7/31	85	22	140	1100	None	None	....	14.9	
8/1	85	22	140	1100	98	None	122	2.5	
8/2-8/6	85	22	140	1100	None	None	145-154	12.7-31.9	
8/7	85	22	140	1100	71	$\frac{1}{2}$ gm. q.i.d.	183	7.0	
8/8-8/13	85	22	140	1100	106	"	142	5.3-7.0	75
8/14-8/23	85	22	140	1100	None	"	138-119	1.0-9.1	
8/24	85	22	140	1100	110	"	126	5.8	
8/25-9/5	85	22	140	1100	110	None	126-160	2.2-6.0	
9/6-10/5	85	22	140	1100	None	None	152-102	1.0-9.7	75-72

He improved steadily. The insulin was increased daily until the blood sugar was normal. A gain in weight from 68 kg. on July 10 to 77 kg. on July 22 followed the alleviation of the ketosis.

*Progress Notes.* Prior to duodenal extract therapy his actual insulin requirement was 106 units daily, given in 4 doses. As will be seen in Table 1, with the blood sugar at 0.103% (July 30) when no insulin was given, a loss of 14.9 gm. of sugar in the urine resulted. On the following day, 98 units of insulin reduced the sugar loss to 2.5 gm. From August 2 to 6, when no insulin was given, the blood sugar steadily increased from 0.122% to 0.183% (August 7), with an average daily glycosuria of 24 gm.

With reduction of blood sugar by insulin, duodenal extract (No. 3041362) was begun in doses of 0.25 gm. q. i. d. on August 7. During 11 days (August 14 to 24) of duodenal extract without insulin an average daily loss of 6.3 gm. of sugar ensued, as compared with 24 gm. before the extract was given. The blood sugar increased but little (0.133% to 0.138%) and then fell to normal.

That this improvement might be due to an improved tolerance irrespective of the extract was considered possible. If this were so then the patient would not be expected to tolerate the former dosage of insulin without hypoglycemic reactions. A higher dosage, 110 units, was given, and no insulin reactions were subjectively or objectively noted. This dosage was continued for 13 days (August 24 to September 5, inclusive), the duodenal extract having been stopped on August 24.

There was an increase in the blood sugar to 0.152% on September 7, after stopping 110 units of insulin on September 5, but it decreased on September 10 to 0.120%, a lower value than obtained when 110 units of insulin were given. There was a slight increase in the sugar loss. After a transitory increase in the blood sugar (0.143% on September 14), normal values were restored (0.102 to 0.122%, September 9 to October 2).

We attribute this improvement, without insulin since September 5, to the duodenal extract administered between August 6 and 25.

Glycosuria, due to a proved low renal threshold, persisted throughout.

A glucose tolerance test on October 5 gave the following blood sugar values: Fasting, 0.113%; 1st hour, 0.177%; 2d, 0.117%; 3d, 0.118%. This test was repeated on November 6, the diet having been increased to protein, 85 gm., fat, 94 gm., carbohydrate, 150 gm. (1800 calories), on October 30, with the following results: Fasting, 0.128%;  $\frac{1}{2}$  hour, 0.166%; 1st hour, 0.147%; 2d, 0.110%; 3d, 0.086%.

Subsequent tolerance tests on November 13, 20 and 27 revealed curves reverting to the diabetic type, the last being: Fasting, 0.146%;  $\frac{1}{2}$  hour, 0.179%; 1st hour, 0.166%; 2d, 0.193%; 3d, 0.154%. The latter course to poorer curves may be due, in part, to a larger diet—protein, 85 gm., fat, 18 gm., carbohydrate, 400 gm. (2100 calories)—begun on November 8.

**SUMMARY OF CASE.** 1. There was an average loss of 24 gm. of sugar and the blood sugar increased from 0.103% to 0.183% when 106 units of insulin were stopped. With the extract, 7 days later, the same amount of insulin was discontinued. A daily average sugar loss of 6.3 gm. followed while the blood sugar increased from 0.133% to 0.138% only, and was followed by a drop to normal, 0.119%. That this was due to improvement in tolerance without any aid from the extract seems unlikely when the patient later tolerated a larger dose of insulin, 110 units daily, for a period of 13 days without insulin reactions.

2. It would appear that the extract continued to exert an effect

in this case for at least 73 days after it was stopped as a normal glucose tolerance curve was obtained, November 6. A progressive decrease in tolerance ensued after this date.

3. There is no evidence that the effect of the extract is added to that of the insulin, but rather that its effect is in abeyance while insulin is being given.

We consider the foregoing as unusual in a young diabetic who was in impending coma less than 3 months previously.

CASE 2.—R. M. (Penn. Hosp. No. 31760), a colored male, aged 44, was admitted to Dr. McCrae's service in a semiconscious condition from diabetic ketosis on September 22, 1933. He had no knowledge of having diabetes until August, 1933, when weakness, anorexia, polyuria, thirst and loss of weight (18 kg. in 6 weeks) were observed. No infection had been present nor was any found on admission.

*Past and Family History.* Unimportant.

*Physical Examination.* Tissues dehydrated; skin dry; blood pressure, 100/60; tongue and pharynx dry; many carious teeth; soft systolic murmur at the cardiac apex; pulse rate, 120; moderate tenderness and rigidity in the epigastric region; height, 69 in.

*Laboratory Data.* The blood serological tests and, beyond a mild leukocytosis, the blood counts were normal. There were heavy reactions for sugar, acetone and di-acetic acid in the urine.

*Progress Notes.* The effect of stopping the insulin before and after giving duodenal extract was observed after his recovery from ketosis. On October 8 no insulin was given and on October 9 a small amount of sugar was lost in the urine. Insulin (32 units) was given on October 9 but was discontinued on October 10. A trace of sugar appeared in the urine on October 13, heavier reactions were found in 2 specimens on the 14th and in 3 on the 15th.

Duodenal extract (No. 3005889) was given, 1 gm. t. i. d. before meals, from October 14 to 23, inclusive. The glycosuria subsided at once.

A glucose tolerance test (October 30) gave the following blood sugar values: Fasting, 0.081%; 1st hour, 0.193%; 2d, 0.196%; 3d, 0.104%. The glycosuria amounted to 4.4 gm.

On November 6, 12 days without the extract, a better curve was obtained: 1st hour, 0.192%; 2d, 0.139%; 3d, 0.060%. There was a loss of 1.7 gm. of sugar in the urine.

The test was repeated on November 20, but through a misunderstanding 75 instead of 100 gm. of glucose were given. Allowing for this there was continued improvement. In fact, we regard the curve as normal. The blood sugar was 0.085% fasting, 0.150% the 1st hour, 0.080% the 2d hour and 0.049% the 3d hour. There was a trace of sugar in the urine. These results were obtained 27 days after the extract had been stopped.

In a test on November 12 (49 days without extract) the fasting blood sugar was 0.089%; the 1st hour, 0.180%; the 2d, 0.165%; the 3d, 0.090%. The test on December 26 (63 days without the extract) was: Fasting, 0.096%; 1st hour, 0.173%; 2d, 0.190%; 3d, 0.139%. Note the increase in blood sugar between the 1st and 2d hours. The glycosuria amounted to 3.7 gm.

Further reduction in tolerance was recorded on April 23, 1934. The peak was 0.224% the 2d hour; 0.144% the 3d hour. The glycosuria amounted to 3.2 gm.

On July 16 (266 days without extract) a still lower tolerance was shown by a curve having a peak of 0.297% at the 2d hour and a 3d-hour value of 0.223%. There was glycosuria (4.8 gm.). At no time was a hyperglycemia found between tolerance tests.

TABLE 2.—DATA IN STUDY OF CASE 2.

Date, 1933.	Diet.				Duodenal extract.	Insulin, units.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
9/22- 9/27	70	110	140	1830	None	40-160	410-158	14.1-8.8
9/28-10/1	70	58	140	1360	None	120-84	207-66	Heavy to 0
10/ 2-10/7	70	91	135	1600	None	90-24	182	0
10/ 8-10/12	70	91	135	1600	None	32-0	...	0 to trace
10/13-10/23	70	91	135	1600	1 gm. t.i.d.	None	84-95	Mod. to 0
10/24, 1933, to 4/23, 1934	70	91	135	1600	None	None	60-118	0*

\* Glycosuria occurred only after ingestion of glucose as noted in case report.

**SUMMARY OF CASE.** Improvement in the tolerance followed the use of the duodenal extract, greatest 27 days after the withdrawal of the extract. Four subsequent tolerance tests showed progressively poorer curves.

During the period of improvement the body weight increased from 67 to 71.8 kg. Further gain (71.8 to 78 kg.) ensued as the tolerance curves became less satisfactory. The increase in weight would tend to depress the tolerance and it might account for the poorer curves obtained on November 12 and December 26, but there was no increase after December 26 yet the tests became less satisfactory. We might expect the gain in weight from October 23 to November 20 to neutralize improving tolerance, but this was not evident.

**CASE 3.**—I. Z. (Penn. Hosp. No. 31768), male Hebrew, aged 65, was admitted on September 23, 1933, complaining of coldness of the extremities and slight swelling about the ankles.

**Present Illness.** The onset of symptoms, polyuria, polyphagia and pruritus, was in 1931. He received no treatment until February, 1933, when he came to the Out-Patient Metabolic Clinic. Examination revealed marked decrease in circulation in the legs and feet due to organic arterial disease.

**Past Illnesses.** Unimportant.

**Family History.** One sister has diabetes complicated with gangrene.

**Physical Examination.** The positive findings were: Height, 64 in.; nutrition good; pupils respond sluggishly to light; marked cyanosis of both legs and feet when in the dependent position, with prompt blanching when elevated and no dorsalis pedis or posterior tibial pulsations in either foot.

**Laboratory Data.** The blood serological tests and the counts were normal. The Roentgen ray examination revealed extensive calcification of the arteries of both feet and the electrocardiogram showed evidence of myocardial disease.

**Progress Notes.** On September 30, after 1 week on a weighed diet (70 gm. protein, 106 gm. fat and 90 gm. carbohydrate—1594 calories), the blood sugar being normal and no glycosuria being found, daily increases of 15 gm. of carbohydrate and the corresponding 60 calories were begun with 1 gm. of duodenal extract (No. 3005889) t. i. d. before meals.

Judging from the glycosuria on admission (it is to be noted that this patient was on the same diet, though estimated, for 4 months prior to admission), it was surprising to find no glycosuria or hyperglycemia when the carbohydrate reached 165 gm. and the total calories 1894 after 5 days of duodenal extract therapy. At this point a glucose tolerance test was given (Table 3). There was no glycosuria.

Further increases in the carbohydrate to 240 gm. on October 9 did not cause glycosuria or hyperglycemia. The diet was held at 70 gm. protein, 106 gm. fat and 240 gm. of carbohydrate (2194 calories) and the duodenal extract was stopped. No significant changes in the blood sugar followed.

On October 17 (7 days without the extract) the tolerance test was repeated. The curve was decidedly diabetic in type (Table 3) and there was glycosuria (1 gm.).

It seemed that with a practically normal curve previously, while he was receiving extract, and a pronounced diabetic type of curve without it that benefit had been secured. The carbohydrate and total calories of the diet were not the same when both tests were given however.

The extract was resumed on October 18; the diet was unchanged, and on October 30 (12 days after the extract was begun) the test was repeated. A decidedly better curve was obtained (Table 3).

On November 3 the diet was increased to 70 gm. protein, 80 gm. fat and 350 gm. of carbohydrate (2400 calories), and on November 6 the duodenal extract was stopped. On November 20 the glucose tolerance test resulted in a decidedly diabetic type of curve, with glycosuria—2.8 gm.

The patient was discharged on December 19, when the first diet (70 gm. protein, 106 gm. fat and 90 gm. of carbohydrate—1600 calories) was resumed. This diet was continued, and on February 2, 1934, another tolerance curve was secured. No extract had been used in the meantime. The curve was that of a pronounced diabetic. Sugar appeared in all 3 urine specimens.

The duodenal extract (No. 3026511) was resumed on February 8, 1 gm. t. i. d., and on February 14 the diet was increased to 70 gm. protein, 165 gm. fat and 110 gm. carbohydrate (2200 calories) and on February 20 the tolerance test was repeated. The curve registered a decided improvement and there was no glycosuria.

TABLE 3.—DATA IN THE STUDY OF CASE 3.

Date.	Tolerance curves, hours.					Duodenal extract.	Diet.				Wt., kg.
	F.*	½.	1.	2.	3.		P.	F.	C.	Cal.	
1. Oct. 5 . .	110	178	174	155	103	Begun Sept. 30	70	106	165	1894	83
2. Oct. 17 . .	100	138	167	165	179	Stopped Oct. 9	70	106	240	2194	83
3. Oct. 30 . .	100	..	166	161	117	Resumed Oct. 17	70	106	240	2194	83
4. Nov. 20 . .	115	..	205	200	194	Stopped Nov. 6	70	80	350	2400	82
5. Feb. 2 . .	129	..	169	..	242	None since Dec. 5	70	106	90	1600	80
6. Feb. 20 . .	89	..	149	170	118	Resumed Feb. 4	70	165	110	2200	80

\* Fasting.

**SUMMARY OF CASE.** While the duodenal extract was being given to a known diabetic increases in the carbohydrate and total calories to the level of a normal diet were made without causing hyperglycemia or glycosuria.

Three tolerance curves, 1, 3 and 6, obtained while the extract was



being given, were all decidedly better than the curves 2, 4 and 5, which were obtained at varying periods after the extract had been withdrawn.

**CASE 4.**—A. B. (Jefferson Hosp. No. WH8386), a girl, aged 13, was admitted to Dr. McCrae's Service on March 31, 1934, complaining of weakness, thirst, poor vision, excessive appetite and frequent urination.

*Family History.* Negative.

*Past Illnesses.* Measles in childhood and frequent "sore throats" prior to removal of her tonsils, in 1929. She has never menstruated.

*Present Illness.* In January, 1934, she noticed an excessive appetite, increased thirst and weakness. In February, polyuria and pruritus vulvæ and in March a blurring of vision became troublesome. On March 15, a physician was consulted; a diagnosis of diabetes was made; a diet was outlined and the patient was improved subjectively. She was referred to the hospital for observation.

*Physical Examination.* Appears drowsy, cheeks flushed, skin dry with a scabetic eruption on face and chest, faint odor of acetone on breath, posterior cervical glands palpable, breath sounds moderately harsh and with impaired resonance over the first intercostal space anteriorly, patellar and Achilles reflexes absent, and a fine tremor of the extremities.

*Further Studies.* Roentgen ray examination, April 14, showed numerous exudative deposits scattered throughout both lungs, believed by Dr. Farrell to be active tuberculous lesions; tuberculin test strongly positive; gastric contents, stools and smears from the pharynx negative for acid-fast bacilli; no sputum obtained; fractional gastric analysis and blood counts normal; Roentgen ray examination, on May 24, revealed no essential change while one on August 17 showed that many of the exudative deposits had disappeared but that characteristics of tuberculous infection remained. The body temperature fluctuated between normal and 100.6° F.

*Progress Notes.* (See Table 4.) A blood sugar on admission of 0.258%, a heavy reaction for sugar, acetone and di-acetic acid in the urine, the acetone odor to the breath, the age of the patient and her drowsiness from ketosis made insulin treatment imperative. Eighty units daily, in 4 doses, were needed.

On April 7, while 80 units of insulin were being given, the duodenal extract (No. 3026853) was begun, 0.5 gm. before meals and at bedtime. A rapid reduction in the insulin was made.

On April 14 the insulin was discontinued. The blood sugar was 0.086% on the morning following the last day of the insulin program, yet on April 16, 2 days without insulin, it was 0.080%.

The diet was increased abruptly on April 17 to 65 gm. protein, 82 gm. fat and 150 gm. carbohydrate (1600 calories), an increase of 5 gm. protein, 22 gm. fat and 60 gm. carbohydrate (460 calories). The blood sugar increased from 0.080% to 0.110% and on April 20 to 0.134%. On April 20 the diet was decreased to 65 gm. protein, 125 gm. carbohydrate and 82 gm. fat (1500 calories), which was still considerably higher than that allowed at the outset of treatment.

The glycosuria ceased and normal blood sugar values were restored.

On May 7 the diet was increased to 65 gm. protein, 135 gm. carbohydrate and 100 gm. fat (1700 calories), and on May 10 the extract was stopped. Neither glycosuria or hyperglycemia resulted. Further increases in diet were made on May 12 and June 12, making the diet 2272 calories. Daily increases of 10 gm. carbohydrate and 40 calories were begun on June 25 and continued until July 8, when the former had reached 295 gm. and the latter 2832. The blood sugar was 0.129% on July 6, following a diet of 80 gm. protein, 265 gm. carbohydrate and 148 gm. fat (2712 calories).

Glycosuria was noted when the carbohydrate reached 295 gm. and the blood sugar reached 0.179%. No extract had been given since May 10.

On July 9 the former diet (80 gm. protein, 155 gm. carbohydrate and 148 gm. fat—2272 calories) was resumed—a sudden decrease of 140 gm. carbohydrate and 560 calories. The blood sugar decreased slightly but subsequently increased to 0.190%—actually higher than with the high carbohydrate, high calorie diet—and there was glycosuria. The effect of the extract was doubtless exhausted.

The duodenal extract (No. 3041362) was resumed on July 9, but it had no effect on the hyperglycemia. Insulin was begun on July 25; 67 units were needed with the low diet to correct the hyperglycemia. This is in contrast to the blood sugar of 0.091% on July 3, seemingly maintained by the extract with a diet of 80 gm. protein, 235 gm. carbohydrate and 148 gm. fat (2592 calories).

The insulin having reduced the blood sugar to normal was stopped. The blood sugar was 0.121% the last day of insulin treatment, while after 1 day without 67 units of insulin it was lower, 0.113%, and after 3 days it was 0.116%.

When readmitted for a repetition of the study, in November, 1934, this patient's insulin requirement was between 60 and 70 units and tubercle bacilli were found in the gastric contents.

TABLE 4.—DATA IN STUDY OF CASE 4.

Date, 1934.	P. gm.	F. gm.	C. gm.	Total Cals.	Insulin units.	Duodenal extract.	Blood sugar.	Glycosuria.
4/ 1-4/ 7 . . .	60	60	90	1140	20-80	0	258-156	29.7-0
4/ 8-4/16 . . .	60	60	90	1140	75-0	½ gm. q.i.d.	117-86	0.0-0.2
4/17-4/19 . . .	65	82	150	1600	0	"	110	0.5-3.7
4/20-5/ 6 . . .	65	82	125	1500	0	"	154-76	5.8-0
5/ 7-5/10 . . .	65	100	135	1700	0	"	99	0.0-0
5/11 . . .	65	100	135	1700	0	0	...	0.0-0
5/12-5/28 . . .	65	124	135	1916	0	0	85-105	0.0-0
5/29-6/11 . . .	70	138	145	2100	0	0	112-99	0.0-0
6/12-6/24 . . .	80	148	155	2272	0	0	98-112	0.0-0
6/25-7/ 8 . . .	80	148	165	2312	0	0	91-129	0.0-0
			295	2832				
7/ 9-7/24 . . .	80	148	155	2272	0	½ gm. q.i.d.	138-179	16.0-0
7/25-8/ 4 . . .	80	148	155	2272	40-67	"	190-105	8.0-0
8/ 5-8/11 . . .	80	148	155	2272	0	"	113-121	0.0-0

Weight increased gradually from 38 to 41 kg. Height, 61 inches.

CASE 5.—C. B. (Penn. Hosp. No. 8897), a colored woman, aged 50, was admitted to the hospital on May 24, 1934, complaining of loss of vision in the right eye, cough and vague abdominal pain.

*Family History.* A distant cousin had diabetes, otherwise unimportant.

*Past History and Present Illness.* She has used sweets freely and tobacco in moderation. She had 1 stillborn child, 2 miscarriages and 1 living child. In January, 1934, following an acute upper respiratory tract infection, a cough, which has remained, became troublesome; she had pains, made worse by coughing, over her right upper chest; small amounts of mucopurulent material were expectorated at night. An attack of pleurisy last winter affected the left chest. Thirst, polyuria, nocturia and pruritus vulvæ were troublesome for 2 or 3 years, while dyspnea on exertion, anorexia, general weakness, failing vision and marked tingling and burning sensations in the toes have been noted recently.

*Physical Examination.* Bilateral cataracts (right nearly mature), few carious teeth, tongue heavily coated, breasts atrophied, limitation of expansion over the right upper chest, a dull note on percussion over the upper lobe, with high-pitched breath sounds, egophony, whispered pectoriloquy, with fine and medium crackling râles anteriorly and posteriorly over the same area, abdominal wall flaccid, a palpable mass the size of a medium grapefruit in the suprapubic region (uterine fibroma) and the blood pressure 98/50

*Further Observations.* The blood serological tests were normal, the Roentgen ray study of the chest revealed multiple cavitations involving the entire upper right lobe, many acid-fast bacilli were found in the sputum, and blood count was: Hemoglobin, 75%; red blood cells, 5,860,000; white blood cells, 11,150; with a normal differential count, and the gastric analysis was normal.

*Progress Notes.* The fasting blood sugar was 0.165% on May 22 and 0.162% on May 25, and there was heavy glycosuria (2%). A diet of 1380 calories was allowed.

The patient's temperature varied from normal to 102° F. The fluctuations were slightly less toward the end of the study. Unfortunately the quantitative tests for sugar were not done before May 29, but judging from the qualitative tests there was no decrease in the glycosuria while the treatment was by diet alone. From May 25 to 31, heavy glycosuria persisted, 24.4 gm. on May 29. In view of the tuberculous infection, the febrile course, the decreasing weight, the increasing blood sugar and the glycosuria, insulin therapy was considered imperative. It was begun on May 30 and continued until June 7. The diet was increased on May 31 to 1600 calories, the insulin was increased to 30 units and duodenal extract (No. 3041362), 0.25 gm. q. i. d., was begun. The blood sugar was 0.209% and there was glycosuria, 4.7 gm.

June 1 to 7, the insulin was increased to 36 units daily, the blood sugar was 0.129% and there was no glycosuria. On June 7 the insulin was stopped. No glycosuria ensued and the blood sugar decreased to 0.110%. The weight remained constant.

The diet was increased on June 13 to 2000 calories. A temporary increase in the blood sugar to 0.135% ensued, but normal values were restored on June 20 and 22. The duodenal extract was stopped on June 22. There was no resulting increase in the blood sugar.

Daily additions of 10 gm. of carbohydrate and 40 calories to the diet were begun on July 6 to determine the limit of tolerance. The blood sugar was 0.110%, July 6 to 17, being 0.110% on July 10, when the diet contained 165 gm. of carbohydrate and 2200 calories. On July 14 the blood sugar was 0.129%, when the diet contained 205 gm. carbohydrate and 2360 calories. Further elevation of the blood sugar to 0.143% occurred on July 18, when the carbohydrate value reached 235 gm., and the calories 2480 on the day previous. Traces of sugar were found in the urine on July 12 and 16.

The duodenal extract was resumed, 0.25 gm. q. i. d., on July 17. July 18 to 24, the former diet (2000 calories), was resumed. Despite this reduction (120 gm. of carbohydrate and 480 calories) plus the use of insulin (resumed, July 19), the blood sugar was higher, 0.166%, on July 21. It was 0.143% on July 23 and 0.153% on July 24. There was, therefore, no decrease in the blood sugar during the 6 days, July 19 to 24, while 36 units of insulin were given daily in 3 doses. The duodenal extract had no apparent effect during this period. July 25 to 31, no insulin was given or subsequently. The blood sugar on July 27 was lower, 0.139%, than when insulin was used. It was 0.139% and 0.137% on July 30 and 31, respectively.

TABLE 5.—DATA IN STUDY OF CASE 5.

Date, 1934.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glyco- suria, gm.
	P.	F.	C.	Cal.				
5/21-5/29 . . . .	70	80	95	1380	None	None	162-165	Heavy
5/30 . . . . .	70	80	95	1380	15	None	...	20.7
5/31-6/ 6 . . . .	70	104	95	1600	30-36	$\frac{1}{2}$ gm. q.i.d.	209-145	4.7-0
6/ 7-6/12 . . . .	70	104	95	1600	None	$\frac{1}{2}$ gm. q.i.d.	129-110	0
6/13-6/21 . . . .	70	140	115	2000	None	$\frac{1}{2}$ gm. q.i.d.	135-113	0
6/22-7/ 5 . . . .	70	140	115	2000	None	None	112-109	0
7/ 6-7/17 . . . .	70	140	125	2040	None	None	110-129	Trace
			235	2480				
7/18-7/24 . . . .	70	140	115	2000	36	$\frac{1}{2}$ gm. q.i.d.	143-166	0
7/25-7/30 . . . .	70	140	115	2000	None	$\frac{1}{2}$ gm. q.i.d.	137-139	0

The weight at the onset was 55½ kg. and on discharge 54 kg.; height, 63½ inches.

**SUMMARY OF CASE.** 1. During the 8 days of insulin treatment the blood sugar fell from 0.209% to 0.129%. This occurred while insulin and duodenal extract were being given.

2. When the insulin was abruptly stopped further decrease in the blood sugar occurred, to 0.110%, presumably due to the effect of the duodenal extract. This effect was repeated during the later stages of the study, when 36 units of insulin were stopped, July 24, the blood sugar fell to a lower level than when the insulin was being given.

3. No glycosuria or hyperglycemia resulted from stopping the duodenal extract.

4. Remarkable increases in the carbohydrate and total calories were necessary to provoke hyperglycemia and glycosuria even though the extract had been stopped.

5. Despite a resumption of the previous lower diet plus insulin there was a continued rise in the blood sugar suggesting that the hyperglycemia had destroyed the effect of the extract or, as seems more likely judging from other cases, its effect was in abeyance while insulin was given.

**CASE 6.**—A. S. (Penn. Hosp. No. 26668), male, Italian, aged 49, was admitted on September 23, 1933. A history of diabetes since 1927 was given when, because of increased thirst and appetite, he had consulted a private physician who found glycosuria. Until his admission, in July, 1932, for treatment of diabetes and a large carbuncle on his back, treatment has been spasmodic.

After his discharge, in 1932, he was treated in the Out-Patient Dispensary save for 7 admissions for treatment of carbuncles.

*Past Illnesses and Family History.* Unimportant.

*Physical Examination.* Well nourished; blood pressure, 135/80; multiple scars over chest, back and neck where carbuncles had been incised. The heart, lungs and abdomen were normal.

*Laboratory Studies.* Blood serological tests normal; red blood cells, 3,320,000; hemoglobin, 85%. Roentgen ray examination of the extremities revealed a moderate degree of calcification of the arteries of both legs.

*Progress Notes.* A history of heavy glycosuria and several blood sugar estimations above normal, the highest being 0.230%, in July, 1932, made it obvious that he had diabetes.

He was given a diet containing 1600 calories, with 110 gm. of carbohydrate on September 23, 1933, and on September 26 daily increases of 10 gm. of carbohydrate and 40 calories were begun and the duodenal extract (No. 3005889), in doses of 2 gm. t. i. d., was started.

There was no glycosuria or hyperglycemia when the carbohydrate reached 260 gm., and the total calories 2187, but a glucose tolerance test (October 5) indicated a very mild diabetes. The diet was then abruptly increased, allowing 350 gm. of carbohydrate and 2557 calories. The blood sugar remained normal.

The extract was stopped on October 9, but the tolerance curve on October 24 suggested that its effect was still operating. The curve might well be interpreted as normal (Table 6) and there was no glycosuria.

On October 30, 100 gm. of glucose were given to this patient by mistake. While no blood tests were made, it is interesting that 6 gm. of sugar were lost in the urine, 34 days after stopping the duodenal extract. Glycosuria had not occurred with the preceding glucose tolerance tests. This contrast may be misleading, as there was at this time a small carbuncle developing on the patient's back. This was freely incised on November 2.

To prevent unnecessary risk the diet was decreased to 1050 calories, with 150 gm. carbohydrate for 7 days, insulin was given and the duodenal extract was resumed. During the course of this infection there was glycosuria and the blood sugar reached 0.205%.

It is perhaps significant that later, March 1 to 19, 1934, a much larger carbuncle appeared during a course of duodenal extract therapy without this apparent loss of tolerance. The diet which had contained 2100 calories, with 175 gm. carbohydrate, from January 20, was left unchanged; no insulin was given but the extract was continued. In this instance the highest blood sugar, the only one above normal, was 0.135% and there was no glycosuria.

On January 15, 1934, 63 days without the extract, and with a smaller diet a poorer tolerance curve was obtained. The blood sugar increased between the 1st and 2d hours and it was above normal at the 3d hour.

On January 22 (70 days without extract) a still poorer curve was obtained. The increase in blood sugar between the 1st and 2d hours was greater, the peak was 0.201% at the 2d hour and the 3d hour blood sugar was 0.174%, the highest 3d-hour value yet obtained.

The duodenal extract (No. 3026511) was resumed on January 22, and on January 31 the glucose tolerance test showed a definite improvement over that of January 22. The peak was lower, the blood sugar remained at practically the same level between the 1st and 2d hours and the 3d hour blood sugar was 0.138%.

On April 10 (after 45 days of extract therapy) further improvement was noted. The curve had its peak at the 1st hour, a greater fall between the 1st and 2d hours and a normal figure at the 3d hour.

The changes which were made in the diet cannot account, we believe, for the curves obtained, neither can the small changes in weight. As for the carbuncles they appeared at such times as to make proof of the effectiveness of the extract most difficult. Especially valuable in our estimations is the curve on April 10, as a very large carbuncle causing fever for several days had intervened between this and the date of the previous test, on January 31.

He was discharged on June 2 and received no extract after June 18. He was readmitted, for a repetition of the study, on November 19, 1934. There was no glycosuria or hyperglycemia nor was there a recurrence of the carbuncles in the interval.

TABLE 6.—DATA IN STUDY OF CASE 6.

Date.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
1932.								
7/20-8/5 . . .	70	40	120	1120	30-36	None	230-100	Heavy-0
1933-1934.								
9/23- 9/25 . .	80	93	110	1600	None	None	114	0
9/26-10/ 6 . .	80	93	125	1657	None	2 gm. t.i.d.	75-92	0
			350	2557				
10/ 7-10/ 9 . .	80	93	350	2557	None	2 gm. t.i.d.	82	0
10/10-11/ 1 . .	80	93	350	2557	None	None	77-189	
11/ 2-11/ 8 . .	65	21	150	1050	6-24	1 gm. t.i.d.	82-205	18-6
11/ 9-11/29 . .	80	93	350	2557	None	1 gm. t.i.d.	68-95	Trace-0
11/30-12/ 7 . .	80	93	350	2557	None	2 gm. t.i.d.	83	0
12/ 8-12/14 . .	75	153	105	2100	None	None	...	0
12/15- 1/21 . .	75	122	175	2100	None	None	101-119	0
1/22- 4/12 . .	75	122	175	2100	None	1 gm. t.i.d.	75-135	0

The weight increased gradually from 63 to 68 kg. Height, 65 inches.

Glucose tolerance tests on November 27 and December 4 were considered normal. There being no object in resuming the extract under these conditions, he was discharged on December 5.

#### Glucose Tolerance Tests.

Year.	Date.	Hours.				
		F.	½.	1.	2.	3.
1933	October 5	84	130	168	154	53
"	October 24	80	...	161	122	82
1934	January 15	119	...	173	184	157
"	January 22	101	...	161	201	174
"	January 31	91	...	155	157	138
"	April 10	82	...	183	123	105
"	November 27	118	188	134	111	75
"	December 4	122	135	188	94	98

**SUMMARY OF CASE.** The duodenal extract seemed to produce better tolerance curves than were obtained without it, and it seemed to prevent the usual loss of tolerance during an acute pyogenic infection. Furthermore, normal glucose tolerance curves were obtained 5 months after stopping the extract. This patient received extract for a longer period than any other.

**CASE 7.**—G. D. (Penn. Hosp. No. 33529), female, aged 8, was admitted on February 19, 1934, complaining of excessive appetite and thirst, polyuria and loss of weight.

*Family History.* Unimportant.

*Past History.* Mumps at 6, scarlet fever and chickenpox at 7, with "ear trouble without discharge" for several days. She had enuresis until the age of 4, and subsequently increased urination with nocturia, nervous-

ness and occasional fleeting pains in the right lower quadrant of the abdomen. Urinalyses done in 1933 were normal.

*Present Illness.* She was well until 3 weeks before admission, when polyuria was noticed. A great appetite and excessive thirst developed and a rapid loss in weight ensued. The urine became syrupy and when dried on clothing left crisp areas. Dr. H. Haines, consulted on February 14, found glycosuria. Improvement followed the adoption of a restricted diet.

*Physical Examination.* Patient undernourished, moderate enlargement of the tonsils and submaxillary glands, posterior cervical gland (right) palpable, heart and lungs normal, small pad of fat in center of the abdomen and blood pressure 105/70.

*Laboratory Data.* Blood sugar 0.203% and urine sugar 4+ (72 gm. in 8 hours). The blood urea and blood counts were normal. The tests for acetone and di-acetic acid in the urine were strongly positive.

*Progress Notes.* It was obvious at the outset that this patient needed insulin, but we wished to observe the effect of the duodenal extract on the hyperglycemia of a child who had never received insulin. The extract was begun at once (No. 3026511 for the first day and No. 3031959 subsequently), in doses of 1 gm., before each meal.

Though the glycosuria decreased, the blood sugar increased to 0.210% and on February 23 to 0.230%. No benefit from the extract being apparent in the first 3 days, insulin was begun.

On February 24 (5 days after admission) the patient had fever, 99.6° F. The temperature remained elevated, during an attack of measles, until March 1. At the height of the fever, 48 units of insulin, given in 4 doses, reduced the blood sugar to 0.098%. A higher dosage, 56 units, was given after all fever had subsided without any evidence of insulin reactions. In view of the prompt gain in tolerance which usually follows the disappearance of fever, we suspected that the extract might be exerting an influence against hypoglycemic reactions in this patient.

On the morning of March 10, a blood sugar of 0.111% was found and the insulin was stopped, an abrupt withdrawal of 56 units. Slight glycosuria occurred until March 16. There was no further loss and the blood sugar values remained normal.

The diet was increased on March 20 and a gradual gain in weight ensued. The patient was discharged on March 24.

The extract was stopped on April 3 and glycosuria appeared on April 24, May 3 and 4. The extract was resumed, 0.5 gm. t. i. d., for 1 week. There was no glycosuria. As it seemed that there was a delayed benefit from the extract lasting from April 3 to 24 we decided to give the extract for 1 week in each month.

From May 5 to 10, inclusive, the extract was given, 0.25 gm. q. i. d., and again from June 1 to 7, inclusive. The blood sugar remained normal and there was no glycosuria. On June 25, 26 and 27, glycosuria appeared but subsided when the extract was resumed, July 1 to 7. Being without active extract we were specially interested in subsequent observations.

Glycosuria returned on July 22 and the blood sugar increased to 0.139% on July 26. Insulin was resumed on August 10; the blood sugar reached 0.239% on September 21 and the insulin requirement has (February, 1935) reached 46 units. A repetition of the study is under way.

**SUMMARY OF CASE.** 1. Judging from her age, weight and laboratory studies, before and after using the extract, the child obviously had a severe diabetes of recent onset. This was apparent before the measles could have altered the picture.

2. We regard it as significant for a child of her physique needing so much insulin during a febrile period to tolerate an actual increase

in the dosage after the disappearance of fever without insulin reactions.

3. There was no demonstrable effect from the extract during the initial 3 days, but later a delayed effect, made possible by the control of the diabetes, seemed to assert itself in an insulin-like action by which it corrected the glycosuria and maintained a normal blood sugar in a patient in whom this would be considered possible only with insulin. The full effect of the extract was not apparent until 6 days had elapsed without insulin.

4. The effect of the extract seems to have lasted, in this patient, about 3 weeks after its discontinuance.

TABLE 7.—DATA IN STUDY OF CASE 7.

Date, 1934.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
2/19- 2/22 . .	45	53	110	1100	None	1 gm. t.i.d.	203-210	72.0-51.6
2/23- 3/ 9 . .	45	53	110	1100	32-56	1 gm. t.i.d.	230-98	6.7-0
3/10- 3/19 . .	45	53	110	1100	None	1 gm. t.i.d.	85-103	3.8-0
3/20- 4/ 3 . .	60	87	120	1500	None	1 gm. t.i.d.	91-112	0-0
4/ 4- 5/ 4 . .	60	87	120	1500	None	None	105-123	0-trace
5/ 5- 5/10 . .	60	87	120	1500	None	1 gm. q.i.d.	111-119	0
5/11- 5/31 . .	60	87	120	1500	None	None	102-129	0
6/ 1- 6/ 7 . .	60	87	120	1500	None	½ gm. q.i.d.	...	0
6/ 8 . . . .	60	87	120	1500	None	None	112	0
6/ 9- 6/30 . .	65	87	130	1560	None	None	129	0-trace
7/ 1- 7/ 7 . .	65	87	130	1560	None	1 gm. q.i.d.	114	0
7/8 -11/30 . .	65	87	130	1560	14-28	None	72-239	0-heavy

Weight increased gradually from 27.2 to 31 kg. Height, 54 inches.

**Summary and Hypothesis.** A child diabetic of 8, another of 13, with active tuberculosis, an adult with active tuberculosis, another admitted in coma, a boy of 16 admitted in impending coma and 2 mild diabetics of the arteriosclerotic group (7 cases in all) are presented to illustrate that the duodenal extract prevented hyperglycemia and glycosuria of any extent after the withdrawal of large doses of insulin and that subsequent great increases of carbohydrate and calories were necessary to produce hyperglycemia and glycosuria. Furthermore, better glucose tolerance curves were obtained with the extract than were obtained without it.

The period of benefit following the withdrawal of the extract varied from a few days to several months.

There is no evidence that the extract is of value in reducing a marked hyperglycemia or that it has any effect when given with insulin, except as stated below, but rather that its effect becomes discernible when insulin is used to control the diabetes and then omitted. Repeatedly, lower blood sugar values were obtained with the extract alone than when it was given in conjunction with insulin.

In 2 patients (1 of whom is reported here) with diabetes of long



standing normal glucose tolerance curves were repeatedly obtained 5 months after cessation of extract therapy.

Neither hypoglycemic reactions nor any other untoward effect were noted. It seemed rather that the extract exerted an anti-hypoglycemic effect when large amounts of insulin were given.

Respiratory quotient studies (not reported here) coincided with the behavior of the blood and urine sugars, increasing as they decreased and decreasing as they increased.

Doses of 0.25 gm. of the extract, given orally, 3 or 4 times daily, were effective.

Of 46 patients who received the extract, 16 were given inert material. Of the remaining 30, 12 had severe and 18 had mild diabetes. Of the 12 with severe diabetes, 8 (4 of whom were children) showed a definite response to extract therapy, while 4 (3 adults and 1 girl of 16) gave no evidence of benefit. Of the 18 mild cases, 11 were helped and 7 were not.

All 4 of the severe diabetics who failed to benefit from the extract belong to the group of diabetics who have an extremely narrow margin of safety between hypoglycemia and hyperglycemia. Other severe diabetics requiring as much or more insulin, but who had a greater margin of safety, gave spectacular response to extract therapy.

The results suggest that 3 types of diabetes exist, *e. g.*, (1) from lack of activation of the pancreatic islands by a duodenal factor, (2) from loss of islands of Langerhans and (3) an insensitiveness of the organism to insulin. The last mentioned may be subdivided to include various endocrinal imbalances.

The prolonged period of apparent benefit after withdrawal of the extract suggests the possibility that the duodenal factor is to the pancreas as iodine is to the thyroid gland. This tentative hypothesis is presented for consideration until we are obliged to alter or add to it in the face of new evidence obtained by a continuation of our study.

The authors are grateful to Parke, Davis & Co., especially to Dr. A. E. Sharpe of their staff, for supplying us with the duodenal extract. We are indebted to Drs. Macallum and Laughton for making the animal assays for us and for their readiness to place at our disposal the results of their studies on this subject. We wish to express our appreciation to the staffs of the Pennsylvania and Jefferson Hospitals, who aided in carrying out this study.

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## NOTE ON THE USE OF SUPRARENAL EXTRACT AND SODIUM SALTS IN A CASE OF ADDISON'S DISEASE.

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PRODUCTIVE research during the past few years has done much to revive interest in the study of Addison's disease, and to elucidate some of its problems. Swingle and Pfiffner,<sup>1</sup> and Hartman<sup>2</sup> have prepared extracts of the cortex of the suprarenal glands which are effective in maintaining the lives of adrenalectomized dogs and have proved of value in treatment of certain human cases. Loeb<sup>3</sup> and Harrop<sup>4</sup> have shown a relationship between sodium chlorid loss from the body and the development of Addisonian crises. Loeb<sup>5</sup> believes that the most satisfactory hypothesis to explain the behavior of the sodium base in suprarenal insufficiency is that the suprarenal glands exert a regulatory effect on sodium excretion.

The following case of Addison's disease is reported because of two points: (1) The failure of cortical extract alone to prevent the development of crisis; and (2) the demonstration that other sodium salts can be substituted for sodium chlorid without detriment.

**Case Abstract.** The patient, aged 25, was sent to the Lakeside Hospital on September 9, 1933, by his family physician because of Addison's disease. This diagnosis was manifest because of conspicuous darkening of the skin, vomiting, weakness and weight loss, all coming on in a period of 3 months. No history of exposure to tuberculosis could be elicited. Past illness was negligible (acute gonorrhea in 1930; measles, diphtheria and influenza in childhood). Four months before admission, he was ill with dry pleurisy for 3 days. He was native born of Polish parents, single, unemployed for 2½ years, formerly a welder.

*Physical examination* showed nothing significant except pigmentation and a blood pressure of 108/55. The skin was uniformly dark grayish-brown with darker spots, 2 mm. in diameter, over each cheek, hard palate, gums, buccal mucous membrane and in the conjunctiva of one eye. A few days later similar spots developed on his forearms and later disappeared while under treatment. Temperature averaged 37.5°, pulse 80 and respirations 22.

The urine was normal except for a low specific gravity (1.012). Hemoglobin (Sahli) 91%, erythrocytes 5,150,000 and leukocytes 8400. The blood smear was normal and the blood Wassermann test negative. Blood sugar 75, plasma chlorid 310 and creatinin 1.5 mg.%. Icteric index 6.

Basal metabolic rate  $-2\%$  of normal. Electrocardiogram normal. Roentgen ray of lungs showed no evidence of old or recent tuberculosis. A plate of the abdomen showed several flaky areas overlying the upper pole of the left kidney. These had the density of calcium salts, and it was believed might represent changes within the adrenal. There were no similar shadows on the right.

Our plan to study his salt metabolism was hurried by a mild crisis. He had been given a full diet, and allowed to salt his own food. On the third hospital day, he suddenly became irrational and vomited repeatedly. His temperature was unchanged, but his blood pressure fell to 80/40. He was given 750 cc. of physiologic salt solution intravenously, with temporary improvement. His chlorid (as Cl) intake the preceding day had been 2.53 and urinary output 3.24 gm.; on this day intake was 4.21 and output 4.03 gm. The following day he again became irrational and vomited. The blood urea nitrogen was 23.6 and plasma chlorids 270 mg.%. He was given 2250 cc. saline solution subcutaneously and intravenously. On the fifth hospital day he was markedly improved, and eating well.

Since it was obvious that he could not keep himself in salt balance by his diet, however salty, he was given additional salt—finally 12 gm. NaCl daily—in capsules. With this additional intake of salt, he ate well and had no complaints. On the ninth night, in a “nightmare” he fell out of bed, breaking a glass urinal and cutting his thigh on a large fragment. This kept him in bed until the twenty-second hospital day, when he felt well enough to walk about the ward. Without sudden change, his blood pressure had come up to 110/75. During this period, his chlorid (Cl) intake, including the calculated amount in his food and that in the weighed amount of NaCl on his trays and in the capsules, varied from 6.66 to 18.06 gm. daily, and his urinary output from 5.22 to 16.8 gm. There was no significant change in weight. Hemoglobin 90%, erythrocytes, 5,200,000 and leukocytes 8100. Blood urea nitrogen was 19.7 and plasma chlorids 335 mg.%.

On the twenty-fourth hospital day, the salt capsules were stopped, but an abundance was provided with his meals which were generous, for he was feeling well. The following day he was “despondent,” the next irritable and remained voluntarily in bed. His appetite was fair, and blood pressure 110/75. On the fifth day without capsules he was worse mentally and was nauseated. His chlorid intake on these days had been 8.5, 6.4, 5.37, 3.09 and 4.87 gm.; his output, 10.81, 10.41, 9.14, 6.6 and 5.45 gm. A crisis was obviously developing, but his blood pressure was 105/80, pulse and temperature normal, fluid intake 1750 cc. and output 1150 cc. There was no demonstrable trouble with his circulation, no water loss or retention and no sign of disordered central nervous system. The blood sugar was 99, urea nitrogen 25.4 and plasma chlorids 317 mg.%. It was then impossible to predict the crisis from any physiologic change, but it was quite apparent to the many observers familiar with his previous behavior that a crisis was impending.

Two days later—on the eighth day after the salt capsules had been stopped—he was clearly in crisis, as shown by low blood pressure (85/55), vomiting, blood urea nitrogen 30.3 and plasma chlorids 292 mg.%. He was given 30 cc. of a potent suprarenal cortex extract\* intravenously during the day, and food and drink with and without salt were urged. There was no improvement. The next day he received 30 cc. eschatin intravenously and 30 cc. intramuscularly without improvement. Since he was getting worse, it was thought dangerous to trust to eschatin alone any longer. He was, therefore, given glucose and saline solution intravenously, with definite improvement in 12 hours and great improvement in 36 hours. He

\* Eschatin—Parke, Davis & Co. Furnished through the courtesy of Dr. E. A. Sharp.

was then put back on a full diet with 12 gm. NaCl in capsules daily. The events of this period are shown in Table 1.

TABLE 1.—EFFECT OF ESCHATIN AND NaCl DURING A CRISIS.

Hospital Day.	Cl intake, gm.	Cl urine, gm.	Blood sugar, mg. %.	B. U. N., mg. %.	Plasma Cl, mg. %.	Hgb., %.	R. B. C., millions.	W. B. C., thousands.	Remarks.
25th . . .	6.40	10.40	76	19.7	335	90	5.2	8.0	Second day without NaCl capsules.
29th . . .	1.09	3.19	99	25.4	317				Sixth day without NaCl capsules.
30th . . .	?	5.06	..	..	..				Crisis impending.
31st (8 A.M.)	?	1.09	79	30.3	292	103	5.8	9.6	In crisis { Before eschatin. After 30 cc. eschatin After 80 cc. eschatin After 20 gm. NaCl.
(9 P.M.)	?	1.06	72	28.0	283				
32d (7 P.M.)	?	1.06	72	40.7	266				
33d . . .	11.37	3.38	90	32.4	280	70	3.9	7.7	Much improved. Apparently out of danger.
34th . . .	10.62	13.49	80	21.1	326				
35th . . .	9.85	15.38	90	13.9	327				

Ten days after this crisis he was up and seemed quite well. All observers agreed that there was fading of the pigmentation of his skin and many of the millimeter-sized patches on his forearms, which had been recorded by mapping, were found to have disappeared. His blood pressure was 105/75.

We wished to study the effect of substituting other chlorids and other sodium salts for NaCl. Consequently, on the sixty-third hospital day, with the knowledge and consent of the patient, the NaCl capsules were stopped, and mixtures of ammonium, calcium and potassium chlorids substituted. On the third day of this medication, he complained of abdominal pain, nausea and vomited. His blood pressure fell suddenly to 90/50, and he was given intravenous saline solution, with good results. The changes in the acid base balance in his serum are shown in Table 2. The effect of of these chlorids can scarcely be estimated, since nausea and abdominal distress developed too soon to say that sodium loss was the cause. Later, while on a full NaCl intake, capsules of KCl were again followed by abdominal distress, but not crisis.

TABLE 2.—EFFECT OF DIFFERENT SALTS ON SERUM ELECTROLYTES.

Date, 1933.	Total base, m.eq.	Cl, m.eq.	CO <sub>2</sub> , m.eq.	Protein, m.eq.	P., m.eq.	Base - Acid, m.eq.	pH.	Remarks.
Nov. 2	148.8	100.8	24.8	16.6	3.5	3.1	7.35	On 12 gm. NaCl daily + salt on food. After 3 days low NaCl, high Cl. After 14 days high Na, low Cl. After 2 days high NaCl.
5	143.7	93.2	21.2	18.7	2.7	7.9	7.40	
Dec. 5	150.4	99.1	25.4	16.6	2.5	6.8	7.38	
9	149.2	100.0	27.3	17.3	2.7	1.9	7.41	

After 14 days of a full diet plus 12 gm. NaCl in capsules, a mixture of Na<sub>2</sub>SO<sub>4</sub>, and Na<sub>2</sub>PO<sub>4</sub> and Na<sub>2</sub>CO<sub>3</sub> containing an equal amount of Na was substituted for the NaCl capsules and he was given a salt-poor diet. He was maintained on this régime for 17 days without discomfort, and with little or no change in his serum electrolytes. His chlorids (as Cl) intake and urinary output fell to less than 1.5 gm. daily. This satisfied us that he could be kept from crisis by other sodium salts as well as by NaCl. He was up and about the ward quite as a healthy, cheerful person. He had,

however, become weary of hospital life and asked for a vacation. He was allowed to go home December 10, on a full diet plus 16 gm. NaCl daily in capsules.

He returned to the Out-Patient Department by appointment, December 20, with a blood pressure of 120/80, feeling strong and with a good appetite. A week later, although he had continued to take the same amount of NaCl, his appetite was not as good and he had been sleepless; blood pressure, 98/65, pulse 84 and temperature 36.3° C. The clinic physician, who had been his ward physician, noted his behavior and thought he was about to have a crisis and sent him into the hospital.

On readmission, January 3, 1934, a general survey of his condition disclosed no new developments, except that his color was lighter and the pigmented spots less numerous. Contrary to expectation, he did not go into crisis but remained well on his salt capsules (16 gm. daily) in addition to a liberal diet. Careful studies of his behavior did show him to be irritable and "unhappy" at times.

After 7 days, we undertook to make further studies of his salt metabolism, but the evening of the first day on this new régime he was found irritable and confused in the night. Since this suggested the onset of crisis, our plans were changed, and he was given saline solution subcutaneously and intravenously, and glucose solution intravenously. The following day with a blood sugar 47 and plasma chlorids 434 mg. %, he was in profound crisis. Signs of bronchopneumonia—râles, dullness and bronchial breathing—became manifest. His temperature rose to 38.5° C., pulse to 120 and respirations 45. In spite of eschatin (20 cc.) and saline and glucose solution intravenously, he died that afternoon. Autopsy was not permitted.

This patient presented a typical picture of Addison's disease of the acute type, in all probability due to tuberculosis of the adrenal glands. In spite of the fact that the disease was advanced enough to lead to a crisis shortly after admission, he was maintained in fair condition for 4 months by NaCl alone, without cortical extract. In one crisis, exhibition of NaCl was sufficient to bring him out, while in a subsequent one, cortical extract alone, even in large doses, was ineffective. This is at variance with the report of Snell.<sup>6</sup> The objection might be raised that cortical extract was withheld too long. It was given as soon as the signs of impending crisis became manifest, at a time when we believe NaCl alone would have been effective.

He remained in good condition when other sodium salts were substituted for NaCl. This supports Loeb's suggestion that one of the phenomena of Addison's disease is an abnormal sodium metabolism. Chlorid intake can be greatly reduced without apparent detriment. It is interesting that in spite of the marked decrease in chlorid excretion—from 16.41 to 1.06 gm. per day on the low chlorid diet, there was little change in his serum chlorids or total base. Finally, in the presence of infection, signs of crisis developed for which all treatment was unavailing.

**Summary.** In a patient with typical Addison's disease clinically, a potent extract of the suprarenal glands alone was ineffective in the treatment of crisis. Other sodium salts could be substituted for NaCl without detriment.

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## HISTOLOGIC CHANGES IN THE ADRENALS OF TUMOR-BEARING RATS.

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AREAS of infiltrating cells have frequently been noted in this laboratory in the course of histologic examination of the adrenal glands and periadrenal fat of young male albino rats bearing the Walker rat tumor, a transplantable malignant tumor of mammary origin which has been regarded as a carcinosarcoma. Similar areas of infiltration have been encountered in a variety of pathologic conditions, including cancer, in man (Paunz<sup>1</sup>).

In the adrenal medulla the infiltrating cells are composed of leukocytes and lymphocytes (Fig. 1), although they sometimes consist exclusively of eosinophilic leukocytes. These cells appear in large numbers within the medullary veins, but are still more frequently found in the neighborhood of the vessels, between the epithelial cells. Occasionally we have observed small homogeneous basophilic granules, which we regard as degenerated lymphocytes.

The same cellular elements are encountered in the adrenal cortex (Fig. 2), in a still larger proportion of glands examined. In this region we have also found accumulations of epithelioid cells, very similar to the adrenal cortical cells except in that they possess a decidedly basophilic cytoplasm. In some cases, infiltrating cells were also found in the periadrenal tissue, the spleen and the liver.

Areas of infiltration have been observed in approximately one-third of a total series of over 130 rats bearing this tumor; since serial sections were not made, the incidence may be higher. These areas, which never occur in normal rats, were not observed in animals which were sacrificed when the primary tumor weighed less than 50 gm. It is, therefore, quite possible that they represent a reaction to necrotic processes occurring within the larger tumors, rather than to the malignant growth as such. This was all the more

likely, since we were able to show in a previous communication that the changes occurring in the pituitary gland of tumor-bearing rats which have been considered as characteristic of cancer are simply the result of tissue decomposition.<sup>2</sup>

In order to test this theory we implanted 10 adult male albino rats, of the same age as those used in the tumor experiments, with fresh kidneys, taken from other albino rats. These implants were made under sterile conditions intraperitoneally at intervals of 3 to 10 days during a period of 49 days; the animals were then killed. Each of them received 12 kidney implants during this period. Although postmortem examination showed that the implanted kidneys were necrotic and had been largely absorbed, and the animals all showed the characteristic histologic changes in the hypophysis which we described in our previous paper, none of them had areas of infiltration in the adrenals. We have to conclude, therefore, that the formation of these areas in the adrenals of the tumor-bearing rat is not ascribable to the factor which produces the characteristic changes in the hypophysis. Since, on the other hand, such areas may very rarely be seen in the adrenals of chronically infected rats, we are not inclined to consider them as characteristic of the presence of living neoplastic tissue.

This view is also substantiated by another experimental series of 12 non-tumor-bearing rats, which were injected (6 subcutaneously and 6 intraperitoneally) twice daily with 2 cc. of necrotic tumor material prepared as follows: The peripheral zones of growing tissue were removed from large tumors weighing from 80 to 150 gm., the central portions, consisting almost entirely of necrotic cells, being placed in the freezer ( $-6^{\circ}$  C.); after repeated freezing and thawing for 7 days, this necrotic tumor material was ground with sand, suspended in 3 volumes of 0.2% aqueous solution of sodium carbonate containing 0.25% tricresol, and centrifuged for 1 hour; the supernatant fluid was then decanted off for injection. These injections did not lead to the formation of tumors in any of the 12 experimental animals; 50% of them, however, developed abscesses at the site of injection and were accordingly sacrificed after 43 daily injections, the rest being treated for 58 days altogether. Histological examination revealed the presence of areas of infiltration in the adrenals in 3 cases, in the spleen in at least 7 cases, and in 1 case in the liver. Degenerative changes in the pituitary, similar to those observed in tumor-bearing rats,<sup>2</sup> were noted in 3 animals of this series.

**Summary.** Areas of infiltration of leukocytes and lymphocytes in the adrenal medulla and cortex of rats bearing the Walker rat tumor are described, and the possible causes of their formation are discussed.

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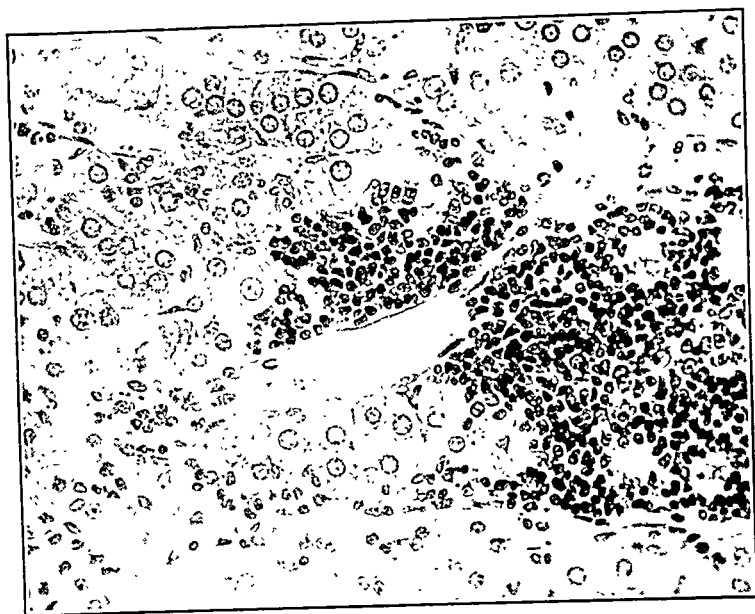


FIG. 1.—Areas of infiltrating cells within the medulla.

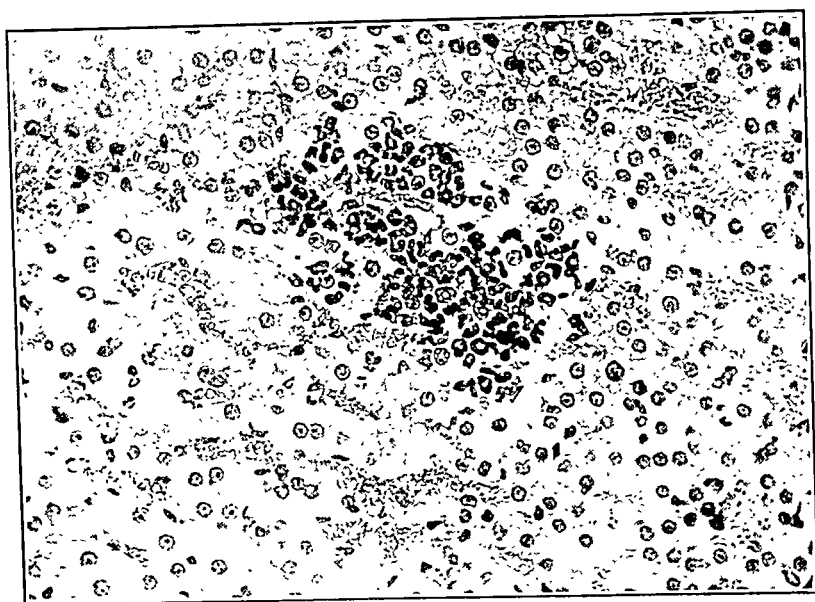


FIG. 2.—Infiltrating cells within the adrenal cortex.





## BENCE-JONES PROTEINEMIA IN MULTIPLE MYELOMA.

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QUALITATIVE and quantitative abnormalities of the blood serum proteins have been reported in occasional cases of multiple myeloma. The occurrence of Bence-Jones proteinemia, associated with hyperproteinemia, is, however, so unusual that even a single case is worth recording.

**Case Abstract.**—T. P., white female, aged 41, was admitted to this hospital, January 8, 1934, service of Dr. McCrae, complaining of severe pains in back, radiating down legs and up left side of body; precordial pain and dyspnea on exertion, that had been present for 3 months. Her previous health had been good.

Physical examination revealed marked pallor, slight enlargement of heart to the left and tenderness over ribs and scapulæ. Pulse, 80 to 120; blood pressure, 140/70; respirations, 22; temperature ranged from 98 to 100° F. during stay in hospital.

**Röntgen ray examination:** areas of bone destruction in 1st, 6th, 7th and 9th ribs, both clavicles, both scapulæ, skull, both humeri and femurs, pelvis, left ulna and right radius. Diagnosis: multiple myeloma.

**LABORATORY STUDIES.** *Urine* (January 17, 1934). Sp. gr. 1012 to 1020; cloud of albumin, few granular casts; Bence-Jones protein in large amounts. Several examinations revealed essentially the same findings.

TABLE 1.—BLOOD CHEMICAL FINDINGS.

Date.	NPN mg. %	Creat. mg. %	Choles- terol mg. %	Ca mg. %	P mg. %	CO <sub>2</sub> capac- ity vol. %	Total protein gm. %	Alb. gm. %	Glob. gm. %
1-18-1934	93.3	6.1	147	12.9	5.8	37	8.7	2.9	5.8
1-31-1934	84.5	6.5	...	9.2	6.8	32	11.3	2.8	8.5

TABLE 2.—BLOOD PROTEIN PARTITION.

Date.	Total protein.*	Alb.*  Grams	Glob.*  per 100 cc.	Precipitated protein (80° C.)	
				By difference.	Direct determina- tion.
1-18-1934	5.5	2.9	2.6	3.2	3.0
1-31-1934	5.7	2.8	2.9	5.6	5.2

\* In supernatant fluid after precipitation at 80° C. and centrifugation.

**Blood Count.** Hemoglobin 28 to 30% (Dare); red blood cells 1,300,000 to 1,900,000; white blood cells 1700 to 4700; differential count essentially normal.

*Wassermann and Kahn reactions* negative.

The patient received three whole blood transfusions of 200 cc. each and left the hospital against advice on February 3, 1934. She was subsequently

admitted to the Philadelphia General Hospital (February 18, 1934) where she died.

The diagnosis of multiple myeloma (granulocytic type) was confirmed at *autopsy*, the report of which was made available through the courtesy of Dr. R. P. Custer. The kidneys showed chronic nephrosis with diffuse interstitial fibrosis and the parathyroid glands were slightly enlarged, showing fatty infiltration on histologic examination.

It is of interest to note that a few days before death (February 27, 1934) the blood creatinin had risen to 13.6 mg. and the serum phosphorus to 12.5 mg. per 100 cc.; the serum calcium was 9.2 mg. while the total serum protein had fallen to 6.84 gm. per 100 cc.

Special studies of the serum for Bence-Jones protein were performed as in the cases reported by Wintrobe and Buell<sup>1</sup> and Shirer, Duncan and Haden.<sup>2</sup>

1. The serum was heated in a water bath. Precipitation was observed to begin at 52° C., gradually increasing with an increase in temperature to 65° C. The degree of precipitation was distinctly less at 85°, increased again upon cooling to 65° and disappeared at 10° C.

2. The serum was heated to 80° C. and was centrifuged at high speed for 20 minutes. The supernatant fluid was removed and was examined for total protein, albumin and globulin. These values are presented in Table 2.

3. The precipitate was washed with and suspended in distilled water and the protein content of the suspension determined. The values obtained for the two specimens were 3 and 5.2 gm. per 100 cc. respectively, being slightly lower than the figures obtained by the indirect method cited above.

4. After washing several times with water, a portion of the precipitate was treated with alcohol of increasing strength, then with absolute alcohol followed by ether and finally it was dried in a vacuum desiccator over sulphuric acid. The white powder thus obtained responded to the usual protein color reactions, was readily soluble in dilute acids and alkalies and precipitated from such solutions upon neutralization. Precipitation occurred in the faintly acid solution at 50° C., was apparently complete at 75° C. and the precipitate went into almost complete resolution upon boiling.

**Discussion.** Attention has been directed in recent years to the occasional occurrence of hyperproteinemia in patients with multiple myeloma. Values for total serum protein ranging from 9.35 to 13.84 gm. per 100 cc. have been reported by Perlzweig, Delrue and Geschickter,<sup>3</sup> Bannick and Greene,<sup>4</sup> Wintrobe and Buell,<sup>1</sup> Shirer, Duncan and Haden,<sup>2</sup> Bönninger,<sup>5</sup> Reimann,<sup>6</sup> Johansen,<sup>7,8</sup> Jores<sup>9</sup> and Kumpf.<sup>10</sup> Qualitative abnormalities of the serum proteins have also been noted by a few observers. Bence-Jones protein or a protein resembling it has been demonstrated in the blood plasma of individuals with multiple myeloma by Ellinger,<sup>11</sup> Askanazy,<sup>12</sup> Jacobson,<sup>13</sup> Abderhalden,<sup>14</sup> Gabbe,<sup>15</sup> Hewitt,<sup>16</sup> Zadek and Lichtenstein,<sup>17</sup> and Shirer, Duncan and Haden.<sup>2</sup> Shirer, Duncan and Haden<sup>2</sup> and Short and Crawford<sup>18</sup> described the formation of a heavy precipitate in the process of inactivating the blood serum at 56° to 60° C. during the performance of the Wassermann test. Wintrobe and Buell<sup>1</sup> observed spontaneous precipitation, at room temperature, of an abnormal protein which, however, did not conform to the recognized characteristics of Bence-Jones protein; furthermore, the latter substance could not be demonstrated in the urine.

The characteristics of the abnormal protein in the blood plasma in the present case correspond closely to those of Bence-Jones protein. It is interesting to note that the substance was precipitated with the globulin fraction (by 22.2% sodium sulphate) in the determination of serum albumin. Similar findings were obtained by Shirer, Duncan and Haden<sup>2</sup> in 2 cases, suggesting the close relationship between Bence-Jones protein and globulin which has been stressed by Hopkins and Savory<sup>19</sup> and Taylor and Miller.<sup>20</sup> The purified preparation gave practically typical precipitation reactions of Bence-Jones protein except for the fact that resolution was not complete at 100° C. This, however, may have been due to the presence of a small quantity of globulin, carried down with the precipitate of Bence-Jones protein.

This combination of hyperproteinemia and Bence-Jones protein in the blood of patients with multiple myeloma has apparently been conclusively demonstrated previously only by Shirer, Duncan and Haden<sup>2</sup> although it probably also existed in the case reported by Jacobson.<sup>13</sup> The frequent failure to detect Bence-Jones protein in the blood is probably due to the fact that its characteristic properties of precipitation at relatively low temperatures and resolution at higher temperatures are by no means invariably exhibited. These phenomena are influenced by several variable factors, including the hydrogen-ion concentration, various electrolytes, organic compounds and the quantity of Bence-Jones protein. Although this substance has been isolated in pure, crystallin form from the urine by Bayne-Jones and Wilson,<sup>21</sup> there is abundant evidence, as stated by Wintrobe and Buell,<sup>1</sup> that it should be regarded not as a chemical individual but rather as a "class of substances which exhibit in common this peculiar precipitation phenomenon." Although the characteristic precipitation at 50° to 60° C. of a protein obtained from blood plasma has been reported by several observers, as noted above, partial or complete resolution at higher temperatures has been reported previously only by Ellinger,<sup>11</sup> Abderhalden<sup>14</sup> and Shirer, Duncan and Haden.<sup>2</sup>

Hypercalcemia has been observed in several patients with multiple myeloma. Serum calcium values ranging from 11 to over 18 mg. per 100 cc. have been reported by Barr and Bulger,<sup>22</sup> Bulger and Gausmann,<sup>23</sup> Jores,<sup>9</sup> Caylor and Nickel,<sup>24</sup> Shirer, Duncan and Haden,<sup>2</sup> Gutman, Swenson and Parsons<sup>25</sup> and Reimann.<sup>6</sup> Of interest in the present case is the fact that the serum calcium concentration of 12.9 mg. per cent fell to 9.2 mg. although the serum protein concentration simultaneously increased from 8.7 to 11.3 gm. per 100 cc. The diminution in serum calcium may have been due in part to the increase in serum inorganic phosphorus but it cannot be satisfactorily explained solely on this basis. One must admit that the hypothesis that hypercalcemia in multiple myeloma is dependent upon hyperproteinemia, although plausible, is far from being well established. The possible existence of a state of secondary

hyperparathyroidism, the excessive mobilization of calcium from involved areas of the skeleton, and the presence of marked renal functional impairment and acidosis are complicating factors of probable importance in this connection. Of particular clinical importance is the fact that both the serum calcium and the serum protein concentrations fluctuated considerably during the period of observation (7 weeks), emphasizing the necessity for repeated studies, particularly when normal findings are obtained.

**Summary.** 1. A case is reported of multiple myeloma (granulocytic type) with severe anemia and renal failure. Bence-Jones protein was present in the urine and was also demonstrated in the blood serum.

2. The total serum protein concentration varied between 6.84 and 11.3 gm. per 100 cc., the Bence-Jones protein being approximately 3 gm. when the total protein was 8.7 gm. and 5.2 gm. when the latter was 11.3 gm. per 100 cc.

3. Hypercalcemia (12.9 mg. per cent) was present at the time of admission, the serum calcium concentration falling to 9.2 mg. per cent while the serum inorganic phosphorus concentration increased from 5.8 mg. to 12.5 mg. and the blood creatinin from 6.1 mg. to 13.6 mg. per 100 cc.

4. The relatively rapid and marked fluctuations in serum protein and serum calcium concentrations in patients with multiple myeloma and the variability of the several factors which determine the characteristic precipitation reactions of Bence-Jones protein emphasize the necessity for repeated studies in such cases.

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## BOOK REVIEWS AND NOTICES

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**PHYSIOLOGY IN HEALTH AND DISEASE.** By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1156, 182 illustrations. Philadelphia: Lea & Febiger, 1934. Price, \$9.00.

THIS book is not only a detailed textbook of normal physiology but also deals with functional changes in pathological conditions. We have here a most fortunate opportunity of benefiting by the knowledge of an experimental physiologist who is willing to apply his research experience to clinical matters.

Too often are physiologists unwilling to discuss the functional changes in abnormal conditions in man; sometimes perhaps because the physiologist is a doctor of science and not a doctor of medicine. It therefore often becomes necessary for the pathologist or the clinician to attempt application of his own perhaps hazy arm-chair knowledge of recent developments in physiology to the clinical conditions that confront him. But in this book, Dr. Wiggers makes these applications for him, in such matters as headache, sleep loss, deafness, clinical motor and sensory disturbances, visceral pains, diseases of the blood, clinical disturbances of respiration and circulation and of the gastro-intestinal tract, hypertension, edema of various clinical types, metabolic and endocrine diseases and many other clinical conditions.

This book is a storehouse of critically selected information both for those who are essentially interested in pure physiology and for those who are clinicians and pathologists. I. Z.

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**HEREDITY AND DISEASE.** By OTTO L. MOHR, M.D., Professor of Medicine, The Royal Frederiks University, Oslo. Pp. 253; 107 illustrations. New York: W. W. Norton & Co., Inc., 1934. Price, \$3.50.

THIS monograph is the outcome of a series of Dunham lectures delivered at Harvard University during the past year. The author states that his book represents an attempt to arouse interest in the rôle played by hereditary factors in bringing about disease conditions. The Reviewer has no doubt but that Professor Mohr has admirably succeeded in his aim. There are discussed in a clear and readable style such topics as the Mendelian law of heredity, the genes, dominance and recessiveness, the basic concepts of the relation of heredity and disease, the mechanism of set determinations; intermarriage, etc. All of these topics are of interest not only to the physician but to the educated layman as well. The illustrations are for the most part well chosen diagrams. It is hoped that this work may prove an introduction to a field that is of constantly increasing importance to medicine, indeed to every field of biology. B. L.

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**THE CONSTITUTION AND ITS REACTION IN HEALTH.** By T. E. HAMMOND, F.R.C.S., Assistant Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 160. London: H. K. Lewis & Co., Ltd., 1934. Price, 7/6.

MUCH of interest and importance to both layman and clinician is to be found in this attempt to recapture appreciation of the importance of the constitution in health and in convalescence. The Constitution in Disease is to be dealt with in another book. Though the author is aware of modern

studies of the constitution (Draper and Hurst even being quoted with approval), Jonathan Hutchinson is his high priest and Hutchinson's "Pedegree of Disease" his Pentateuch. A characteristically British sanity warns convincingly against excesses of fresh air, sun, bathing and exercise and sagely advises about the differences in the rules of health at different ages and for the hyposthenic and hypersthenic types. Though there is too much deduction from analogy and few would accept today such opinions as that the full moon has an effect upon those with mental disorders, or that mercury and gold act beneficently on the centers of energy, nevertheless the book as a whole emphasizes forcibly a point of view that today sadly needs forcible emphasis.

E. K.

**TUMORS OF THE FEMALE PELVIC ORGANS.** By JOE VINCENT MEIGS, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Surgeon to Out-patients, Massachusetts General Hospital, etc.; with a foreword by ROBERT B. GREENOUGH, M.D., President-elect of the American College of Surgeons, 1933-34; etc. Pp. 533; 261 illustrations, some in colors, and 49 tables. New York: The Macmillan Company, 1934. Price, \$6.00.

In this thorough exposition of the new growths of the female pelvis, Dr. Greenough states that no other group of tumors has created so much interest in their relation to the glands of internal secretion, and no other group has benefited as much by the use of radiation. A discussion of etiology, diagnosis, pathology and treatment—based upon a wide clinical experience—precedes a full pathologic and follow-up study of a fair sized group of cases from the Massachusetts General Hospital, and a discriminative sifting of the literature upon the subject. The clinical teaching is eminently sound, the pathology is copiously illustrated by many color plates and photographs and well executed. The literary references are carefully chosen and as well.

Of particular interest is the section on rare tumors of the ovary, the malignant embryonal types, disgerminomas and arrhenoblastomas. The section on cancer of the cervix uteri is most complete. The section on treatment and follow-up deductions based upon tumor type is excellent.

The use of the classification of the American College of Surgeons affords a comparable value for the results shown. This is a triple offering for the use of the gynecologist or surgeon, the pathologist and the roentgenologist and should be of much practical service to any of the three groups.

P. W.

**THE HEART VISIBLE. A CLINICAL STUDY IN CARDIOVASCULAR ROENTGENOLOGY IN HEALTH AND DISEASE.** By J. POLEVSKI, M.D., Attending Physician and Cardiologist, Newark Beth Israel Hospital. Pp. 207; 122 illustrations. Philadelphia: F. A. Davis Company, 1934. Price, \$5.00.

THE author states that this book is for the radiologist who has the scientific curiosity of a clinician and for practitioners who do not realize the value of a roentgen examination in cardiovascular conditions. Though he states that most of the films and tracings have been verified at autopsy, throughout the book he neglects to indicate which cases are so confirmed. Some of his conclusions do not agree with my impressions but the lack of autopsy confirmation leaves one unable to determine whether the author was correct in his premises. Under "General Considerations and Methods of Roentgenologic Studies," the author has left out a considerable amount of information that the radiologist who is unfamiliar with this subject

would desire. It should be said, however, that if one reads carefully through the entire book, most of the things that I have reference to are either mentioned in the text or shown in the illustrations. The use of barium studies is not adequately explained; the use of various postures in demonstrating cardiac lesions is not touched upon; the use of the Bucky diaphragm is excluded. Mediastinal and vertebral lesions are not considered. Possibly the Reviewer is a little too critical in this comment, but many of these procedures have long been a valuable routine among radiologists in large institutions. The author, in discussing fluoroscopy, does not emphasize the necessity for well accommodated eyes, especially in the demonstration of sclerosis of the coronary vessels or calcification of the valves. The author then considers the normal heart, abnormal heart, pericardium and great vessels. There is an extensive bibliography after each chapter, but nowhere is it referred to in giving credit to the original authors. One is struck with the great predominance of foreign authors in the bibliography even though well-known American authors have noticeably escaped the author's attention. The chapter devoted to congenital heart lesions is relatively small. Under the great vessels the author did not include the rather important subject of dissecting aneurysm. The illustrations, diagrams and print used in this book for the most part are excellent. It should find a certain demand, but the radiologist who looks to have the subject of cardiac radiologist thoroughly covered will be disappointed. E. P.

BENIGN ENCAPSULATED TUMORS IN THE LATERAL VENTRICLES OF THE BRAIN. Diagnosis and Treatment. By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, Johns Hopkins University. Pp. 189; 83 illustrations, 2 tables. Baltimore: The Williams & Wilkins Company, 1934. Price, \$4.50.

DANDY reports on 40 benign encapsulated tumors in the lateral ventricles, 15 of which are his own personal cases, and 25 are collected from the literature. In addition he mentions briefly 7 small tumors of the choroid plexus and a small group of malignant tumors of the lateral ventricles.

He concludes that there is no syndrome characterizing the benign ventricular tumors and expresses "a very serious doubt that a clinical syndrome for tumors in the lateral ventricles can ever be established." In the last analysis the diagnosis depends on ventriculography which accurately locates the tumor and provides the surgeon with important information concerning the approach to the tumor by operation. In Dandy's 15 cases, localization was made by ventriculography in 11, by ventricular estimation in 2, by neurologic signs in 1 and by a misdirected cerebellar operation in 1. The changes produced in the ventricular system by tumors in the lateral ventricles are: (1) A border or filling defect of the tumor; (2) hydrocephalus; (3) deformity and dislocation of the ventricular system. Dandy says, "Absolute precision in localization of the tumor by ventriculography must dictate the exact site of the operative exposure. A misplaced exposure is certain to be productive of extensive injury to the brain and will probably end in a fatality."

The operative mortality in Dandy's series was 20% with no deaths in the last 7 cases and no recurrence in the last 12 cases. The longest survival is 15 years, the next 13 years. Dandy thinks recurrence will be unlikely.

The pathology of these tumors is varied. Four arose in the glomus of the choroid plexus; 1 was an angioma, 1 an adenoma and 3 others are classified as "pure fibromata of the choroid plexus." The other tumors were not easily classified, being different from all other intracranial tumors excepting some arising from the third ventricle. They are encapsulated



and often attached to the ependyma. Their encapsulation and failure to recur led him to classify them as benign. Their histologic features are more or less disregarded from this standpoint.

The illustrations are clear and convey a good deal of valuable meaning, but the case reports are poorly constructed. Articles are frequently omitted and the style of the case reports recalls too vividly many cryptic hospital case records. The pathologic study of the specimens leaves a great deal to be desired, but as Dandy himself says, he must "defer the ultimate microscopic classification to more competent students of pathology." The tumors represent an interesting group but the report might easily have been included in a single article rather than a monograph.

B. A.

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DIÄTHERAPIE DER LUNGENTUBERKULOSE. By DR. MAX GERSON, Wien, Mit Röntgenbefunden und einem Röntgenkapitel von DOZENT DR. FELIX FLEISCHNER, Wien. Pp. 619; 154 illustrations. Leipzig: Franz Deuticke, 1934. Price, M. 36.

In this comprehensive work the author presents the principles, practical application and clinical results of his dietary therapy for pulmonary and other forms of tuberculosis, which is known as the Gerson diet, and describes those difficulties and complications which necessitate modifications of the diet in particular conditions. Emphasis is placed on favorable results in severe and very severe cases which had either failed to benefit by previous surgical procedures or in whom such procedures were impracticable.

The author has treated about 650 cases of pulmonary tuberculosis with the Gerson diet during the past 11 years, most of which were ambulatory patients. In 1932 Prof. Zondek placed for 1 year 25 pulmonary cases of the Urban Hospital, Berlin, under the author's direction. These cases were selected by Freund and Zondek as patients regarded as therapeutically uninfluenceable, but the study was interrupted by the National Socialist Revolution.

No accessory therapies of any kind were employed. The medication consisted of administration of phosphorized cod-liver oil, Gerson's mineral mixture, calcium bromid, caffein enemas, and a few patients received, in addition, hormonal preparations (vigantol, codein and coagulen) occasionally. Twenty-six private cases are also described in great detail.

The blood chemistry was followed in all cases and roentgenograms were taken at regular intervals of 3 to 7 weeks, all of which were interpreted by Fleischner of Vienna. In a chapter on "The Anatomic and Roentgenologic Morphology of the Curative Processes in Pulmonary Tuberculosis," atelectasis receives special consideration.

No less than 29 chapters are devoted to theoretical and practical considerations relating to predisposition, immunity, anaphylaxis, allergic diseases associated with tuberculosis, exacerbations, dietary therapy as an antiallergic treatment, tuberculous inflammation and the tissue reaction and edema, acid and alkaline therapy, demineralization and transmineralization, the mineral metabolism, etc.

The theoretical part is followed by full details of the practical application of the Gerson diet, the medication, accessory therapies, etc. Here it may be well to point out that the author has repeatedly modified the Gerson diet since its first introduction in 1923 and that he claims for the latest modification, which dates from 1932, better and quicker results than for the previous forms of this dietary.

The application of the present Gerson diet with its four phases and numerous substages is very laborious and complicated; it behooves us therefore to inquire whether the results which this therapy is capable of

yielding justify these efforts. The author points out that the results mainly based on 51 cases of pulmonary tuberculosis with cavitation were obtained under climatically unfavorable conditions in cities, and that a more favorable environment would probably yield even better results because altitude, isolation, etc., would tend to support the dietary therapy.

Of the 51 cases, 5 (10%) were mild ones, 5 (10%) moderately severe, 23 (45%) severe, and 18 (35%) very severe. The 41 severe cases involved tissue destruction of so far-reaching a nature that the literature contains only a few references to similarly favorable results in such cases. Particularly 8 of the 18 very severe cases showed results which the author regards as of fundamental importance because they illustrate possibilities in the cure of tuberculous lung tissue which have so far been underestimated by anatomists.

On the basis of his entire experience the author claims that the Gerson diet is capable of curing the most severe forms of pulmonary tuberculosis and that even cases which have hitherto been regarded as hopeless can be saved by it. On the other hand, the diet must not be regarded as a prophylactic against renewed infection unless it is followed by adequately prolonged suitable dietary after-treatment. The author states that the dietary treatment, if carried out as directed, must necessarily show the patient's improvement (influence on cavities) in the roentgenograms, though the time in which this manifests itself will vary greatly.

The claims advanced by the author are not in line with the results obtained by the majority of the clinicians who applied the older forms of the Gerson diet in pulmonary tuberculosis. Nevertheless, having regard for the modification of the diet and the impressive material which is now presented, this book should prove of interest to clinicians, and suggests the desirability of further study of the diet. Comprehensive authors' and subject indexes and numerous references to the literature are given.

E. M.

FRANKLIN PAINE MALL, ANATOMIST. By FLORENCE RENA SABIN. Pp. 342; 6 illustrations. Baltimore: The Johns Hopkins Press, 1934. Price, \$2.75.

THE author, who worked for 20 years under Mall at Baltimore, having prepared for the National Academy of Science an analysis of his scientific activities, has now, at Dr. Welch's suggestion, prepared Mall's biography, a companion volume to McCallum's *Halsted*. After an unpromising start in our Mid-West, she tells us how he was fortunate enough to go to Germany for postgraduate study in "the golden age of the German University." First studying ophthalmology at Heidelberg, he moved on to anatomy and embryology with His and especially to physiology with Carl Ludwig, from which two men he caught the inspiration that he so richly passed on to others. There he became steeped in a thoroughly congenial scholarly atmosphere that bore its important fruit, when, in 1893, he was invited to organize the department of anatomy at the new Hopkins Medical School. His teaching was to be of the elbow, inductive variety (only partly because he was a poor lecturer) and the teacher, even in his students' routine dissections had always to be the investigator. He did not regard his reforms in the teaching of anatomy as "Germanizing the dissecting room," but rather as "dependent more on what Huxley did and said." (Letter to Arthur Keith.) "Your body is your own text book" is excellent self education for the good students, but one might interpolate that his attitude toward the poor ones (like his remark to his wife as he watched her bathe her baby, "Why don't you just throw her in and let her work out her own technique?") could hardly produce satisfactory results, nor

did he expect it to or seem to care. Severely critical and caustic at times, yet amusing and kindly at others, this complex personality has been deftly handled by Dr. Sabin. As his "character of teaching" she takes L. C. Miall's assertion: "The spirit of enquiry is only to be communicated by those who habitually enquire themselves." The story is interesting and authoritative—the mistakes few: As far as I know, Shippen never spelled his name with an "a" and it is surprising to see him linked with Leidy as a contemporary. This story of a great investigator's development should be of special interest to medical readers as it coincides with the most important change in medical education that this country has experienced in more than a century.

E. K.

**THE BRAIN AS AN ORGAN.** Its Postmortem Study and Interpretation. By FREDERIC WERTHAM, M.D., Formerly Associate in Psychiatry, Johns Hopkins Hospital and Medical School, etc., and FLORENCE WERTHAM, Formerly Charlton Fellow in Medicine, Johns Hopkins University, etc. With an Introduction by ADOLF MEYER, M.D., Psychiatrist-in-Chief, Johns Hopkins Hospital. Pp. 538; with text illustrations and 166 plates. New York: The Macmillan Company, 1934. Price, \$7.50.

THE several texts on neuropathology that have appeared during the past two years indicate a revival of interest in the structural pathology of the nervous system. The present book is a valuable addition. As the title suggests, this work is an attempt to integrate neuropathology, to consider the brain as an organ rather than as a composite of many more or less independent loci of nervous activity. This point of view is presented in a stimulating introductory chapter from which the following may be quoted: "It is not exaggeration to describe current practice by saying that general pathologists study the human organism as a body without a brain, while neurohistologists study the brain as an entity without a body. General pathologists have been inclined to regard the brain as any organ so far as technical methods are concerned, but as something totally different in respect to the interpretation of lesions. Just the opposite should be done. The dissociation of neuropathology from general pathology was perhaps inevitable until it had formulated its own problems and worked out its own methods. The next step, in our opinion, must be a closer union with general pathology."

This indeed is as it should be. Several chapters are devoted to the technique of macroscopic and microscopic examinations of the brain, and to discussion of the kinds of lesions of the nervous parenchyma and their distribution.

B. L.

## NEW BOOKS.

*Diabetes Mellitus and Obesity.* By GARFIELD G. DUNCAN, M.D., C.M. (McG.), Associate in Medicine in the Jefferson Medical College, Philadelphia; Assistant Physician to the Pennsylvania Hospital, etc. With an Introduction by THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, etc. Pp. 215; 9 illustrations and 40 tables. Philadelphia: Lea & Febiger, 1935. Price, \$2.75.

*Stammering and Allied Disorders.* By C. S. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (ENG.). Pp. 182. New York: The Macmillan Company, 1935. Price, \$2.00.

*A Summary of the Treatment of Fractures and Dislocations.* By R. BROOMHEAD, M.B. (LEEDS), F.R.C.S., Surgeon, Orthopedic Department, General Infirmary at Leeds; Consulting Orthopedic Surgeon, St. James's Hospital, Leeds, etc. Pp. 39, mostly tables. Leeds: Jowett & Sowry, Ltd. (Printer). Price, 3/6 including postage, from Mr. Henry Walker, Briggate, Leeds.

*Poliomyelitis.* A Handbook for Physicians and Medical Students. By JOHN F. LANDON, M.D., Attending Physician, Willard Parker Hospital; Special Consultant in Pediatrics, Woman's Hospital, New York, etc., and LAWRENCE W. SMITH, M.D., Pathologist, Willard Parker Hospital, etc. With a Section on the orthopedic after care of the disease by GARRY DEN. HOUGH, JR., M.D., F.A.C.S., F.A.A.O.S., Attending Orthopedic Surgeon, Shriners' Hospital for Crippled Children, Springfield, Mass. Pp. 275; 18 illustrations. New York: The Macmillan Company, 1934. Price, \$3.00.

*The Clinical Aspects of Visceral Neurology.* With Special Reference to the Surgery of the Sympathetic Nervous System. By W. K. LIVINGSTON, M.D., Clinical Associate in Surgery, University of Oregon Medical School. Pp. 254; 46 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, \$5.00.

*The Technique of Post Mortem Examination.* As Practised in the Pathological Institute of McGill University at the Royal Victoria Hospital, Montreal. Compiled by D. R. COMAN, M.D., C.M., Assistant to the Instructor and Demonstrator in Pathological Anatomy. Pp. 47; 12 illustrations. Montreal: Renouf Publishing Company, 1934. Price, \$1.40.

*Medical Tactics and Logistics.* By COLONEL GUSTAVUS M. BLÉCH, Medical Reserve Corps, U. S. Army, and COLONEL CHARLES LYNCH, Medical Corps, U. S. Army, Retired. Pp. 205. Springfield, Ill.: Charles C Thomas, 1934. Price, \$4.00.

*Report on Seventh International Congress of Military Medicine and Pharmacy, Madrid, Spain, May-June, 1933.* By WILLIAM SEAMAN BAINBRIDGE, CAPTAIN, M.C.-F., United States Naval Reserve; Member of the Permanent Committee, Delegate from the United States. Pp. 88; illustrated. Menasha, Wis.: George Banta Publishing Company, n.d. (Price not given.)

An interesting report covering medical services in wartime, military vaccination, preserved foods, dental, veterinary and similar topics. E. K.

*One Hundred and Fifty Years of Publishing, 1785-1935.* [Henry Charles Lea]. Pp. 42; illustrated. Philadelphia: Lea & Febiger, 1935.

*Die Werke des Hippokrates.* Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. GEORG STICKER, Würzburg. Part 3: Die Diät (Lebensordnung) 1. und 2. Buch (Price, Rm. 2.50); Part 4: Die Diät (Lebensordnung) 3. Buch. Die Träume / Die gesunde Lebensordnung (Price, Rm. 2.10). Pp. Part 3, 96; Part 4, 80. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca Rm. 100, card binding.)

*The Medical Clinics of North America, Volume 18, No. 3 (New York Number, November, 1934).* Pp. 301; 17 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, per clinic year July, 1934, to May, 1935, Paper, \$12.00, Cloth, \$16.00.

# PROGRESS OF MEDICAL SCIENCE

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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### STUDIES ON STAPHYLOCOCCI.

CONSIDERABLE progress has been made recently in our understanding of the pyogenic cocci and the many types of infection they produce. Last year studies on hemolytic streptococci were considered and this year we are giving a similar discussion of the staphylococci. Staphylo-toxin has more or less dominated the investigations in the last few years, but many phases of the problem of staphylococcal infection have been stimulated and better methods for classification and biologic studies have been developed.

**Differentiation.** *Pigment.* The recognition of the pathogenic and virulent strains of staphylococcus has always been difficult, since no fully satisfactory criteria for the purpose have been at hand. Thompson has attempted a division into three groups, chiefly on morphologic differences but, although this may help to eliminate certain larger forms which are of little significance in infection, it can be of little help to the larger problem. Although the aureus strains have long been considered as of exclusive importance, this view cannot be held too rigidly today. It is well recognized that several of the strains used by investigators for the production of toxin give white colonies (Nélis *et al.*) or white substrains (Bigger). Burnet used a white variant as the standard toxicogenic strain, and Parish, O'Meara and Clark found the lightly colored aureus better than the deeply colored parent strains.

Pinner and Voldrich reported the derivation of *Staphylococcus albus*, *citreus* and *roseus* from pathogenic cultures of *Staphylococcus aureus*. The albus strains could be changed back to aureus strains by long growth in the presence of antialbus serum. These derived strains were all apathogenic strains. These authors believe "it may be wise not to dismiss too lightly the finding of *Staphylococcus albus* in human tissue or body fluids" and the Reviewer agrees that the evidence from toxin and other products of staphylococci sustains this view. Hoffstadt and Youmans further describe the dissociation of a virulent *Staphylococcus aureus* into a number of colony forms with or without color changes and differences in speed of fermentation and substances fermented, with loss in all of the virulent feature of the original, but

with antigenic specificity by the agglutination and complement-fixation tests. They suggest that mixtures of these forms in cultures may account for the irregular findings in fermentation and other tests and that the avirulent form may remain in the body and, when virulence returns, produce lesions. In a more recent article these writers have discussed the genetic significance of such dissociants. Panton, Valentine and Dix have shown that the pigment, resembling carotin, has by itself no local or general effect in rabbits and that humans, sensitive or not to staphylococci, gave no reaction to it. Goadby found the removal of the lipid material by alcohol and ether did not affect the antigenic power of the staphylococci to produce agglutinins but benzylation prevents agglutinin production for the intact cocci. It will be generally agreed that the pigment responsible for the aureus color is not the determining factor in the infectivity of staphylococci, but the high incidence of *Staphylococcus aureus* in human and animal infections must not be lost sight of in the search for useful criteria of pathogenic strains. Most investigators have noted the frequent correlation of pigment with other characters of significance in infections. Chapman *et al.*, after a study of some 5000 strains, have stressed the importance of an accurate determination of the color production in recognizing the toxic types of staphylococci along with hemolysis and coagulase activities.

**Cultural Methods.** Hughes studied the growth requirements of *Staphylococcus aureus* and separated an activating substance from meat extract, belonging to the chemical group of "natural bases" which was heat stable in slightly acid or neutral solutions but rapidly destroyed in alkaline solution, was dialyzable through collodion membrane and, when added in an amount less than 1 mg. to 50 liters of synthetic media, activated the latter and gave a good growth of staphylococci. Such a medium should serve as a valuable means for more careful analyses of many of the biochemical activities of these cocci. Birch-Hirschfeld used the culture method of Jacobsthal in which a layer of cellophane covers a thick agar plate. The easily dialyzable substances pass through the cellophane and serve as the medium for the staphylococcus and on which it produces hemolysin, protease and other substances in about 24 hours in larger amounts than on ordinary media. Autolysis occurs in a few days and it is recommended for obtaining autolysates of staphylococci. Clifton noted that cultures of *Staphylococcus aureus* in broth develop and maintain rather intense reducing conditions. Following lysis by bacteriophage the potential increases to a more positive value. He gives data which suggest that the observed oxidation-reduction potentials are a resultant of the metabolic activity of the cells. A great deal has been learned about the cultural conditions which favor the production of toxic substances. Bigger demonstrated that the reaction during growth is of fundamental importance and showed that the various methods—the presence of phosphate buffer, of carbohydrates or of both, or culture in an atmosphere containing added  $\text{CO}_2$ —all depend on their buffer action in preventing too great an alkalinity. However, he found that for some strains the carbohydrate (glycerol) method with buffer is superior and with others, the  $\text{CO}_2$  method, and further that there are strains for which  $\text{CO}_2$  is definitely prejudicial. (See also Nélis *et al.*, Burnet and many recent investigators.) It is clearly evident that many *in vitro* conditions alter and determine the metabolic activity of staphylococci and how these can be correlated with those liable to occur *in vivo* is a matter for

much speculation. Reduced oxygen tension is often present in injured tissues, buffers and carbohydrates are available in varying degrees but there is no certainty as to just what the conditions may be in the great variety of infections by staphylococci.

**Modes of Infection.** There have been a number of interesting observations relating to modes of infection. Duran-Reynals describes a soluble factor from invasive strains of staphylococci, after autolysis or extraction, which markedly increases the permeability of tissues and enhances the infections produced by these organisms. This factor was studied on 53 strains of staphylococci from human lesions and was found to be closely correlated with aureus characters, hemolytic power and liquefaction of gelatin. Variants toward the albus type were noted in old cultures; the typical R forms, showing cultural changes, were no longer invasive and had no spreading factor but sometimes a white variant retained a number of other characters as well as the invasive and spreading power. He further showed that the spreading factor enters the blood from the local site and increases the permeability of at least the skin and thus may enhance infections by the same or other bacteria in other regions. It differs from aggressin in being non-specific, thermostable and non-antigenic. The tentative inference drawn from his experiments is that virulence and invasiveness are not the same thing. In a later article he discusses the influence of testicle extracts which contains a similar spreading factor and shows that lesions produced by invasive strains of staphylococci in high dilutions or by non-invasive strains at moderate dilutions are definitely lessened in severity or even suppressed by this factor. These studies serve to explain what may happen in certain types of staphylococcus infection. Menkin<sup>1</sup> demonstrated that the trypan blue injected into an area of cutaneous inflammation induced by *Staphylococcus aureus*, 1 hour after the introduction of the cocci, failed to spread to the tributary lymphatics, while this blockage did not occur with pneumococcus Type I until after 6 or more hours nor with *Streptococcus hemolyticus* until 30 or 45 hours. This difference is explained by the early production of a fibrin network or thrombosis of the lymphatics by the former organism. A further study<sup>2</sup> of these phenomena showed that filtrates of *Staphylococcus aureus* fixes trypan blue in the skin of rabbits by causing occlusion of lymphatics and coagulation of interstitial plasma but after heating to 58° C. for 1½ hours does not do so. This filtrate unheated causes swelling, vacuolation and often degeneration of leukocytes suggesting its similarity or identity to leukocidin. The fixation, therefore, seems to be referable to the irritating property of the organism *per se* and also to the damaging effect of this toxin-like product. Sullivan, Neckermann and Cannon studied the localization and fate of staphylococci after intravenous injection in rabbits, finding a rapid removal from the blood, particularly in the liver and spleen and an ingestion and destruction by the phagocytes. The primary localization occurs in organs with many macrophages and a sinusoid type of blood flow, whereas practically none occurs where the macrophages are few and where the blood flow is rapid in vessels with ordinary endothelium. Active intravenous immunization has little or no effect on the comparative localization but leads to a more rapid removal and death of the bacteria due to the stimulation of mesenchymal tissue with an elevation of the functional state of the macrophages. (See a later discussion on the effect of bacteriophage.)

**Antigenic Toxic Factors (Staphylocoagulase.)** Filtrates of staphylococci have received the major attention of investigators during the last few years and the antigenic toxic factors have been very fully studied. Staphylocoagulase and its action on oxalated or citrated plasma, a characteristic product only of staphylococci, was for a long time thought to require the presence of living cocci for its manifestation *in vitro*, but Gross found it present in filtrates but only of certain strains. He reported it as the first character to appear in cultures; it is heat stable, resisting 70° to 80° C., it disappears from old cultures and he considered it different from the true toxin of staphylococcus. Van Breuseghem used for its study collodion tubes filled with oxalated plasma which were immersed in tubes of the same medium. After seeding the inner tube he noted complete coagulation in 1 or 2 hours followed by a fibrinolysis complete by the next day. The uninoculated exterior plasma is never coagulated, showing coagulase is not dialyzable. Oxalated plasma by itself changes at 37° C., due to alkaline changes, so that it becomes non-coagulable by calcium, but at first it is still coagulated by thrombin, but the plasma in the outer tube is protected by the dialyzable acid from the staphylococcus growth in the inner tube. The plasma thus altered in coagulability is, when seeded with staphylococci, coagulated but not fibrinolysed. Gengou has studied this phenomenon particularly and has determined that it does not need the presence of the constituents of thrombin. He gave evidence that the responsible substance for coagulation and fibrinolysis of oxalated plasma is a fibrinolytic agent secreted by the bacteria even in media free from fibrinogen such as broth; that it acts on pure fibrinogen but the stage of clotting is very short; and that in the plasma the prolongation of the clotting stage is due to the marked antilytic action of albumin and the lesser action of globulin. Finding the agent to be completely or largely retained by filters, he made use of its resistance to heat to obtain bacteria-free preparations after nearly all the cocci had been previously removed by centrifuging. The agent is resistant to age and desiccation, is heat stable (60° C. for 30 minutes), does not dialyze and is practically retained by filters. Gross<sup>2</sup> showed that only staphylococci among pathogenic germs have this power, and it is so markedly characteristic of *Staphylococcus aureus* that it serves as a useful test for dividing the pathogenic from the non-pathogenic strains. Chapman *et al.* found coagulase of great value along with hemolysin and color development for the same purpose. Gross found it to be highly resistant to heat—1 hour at 90° C. and in a few even at 100° C. only weakening it. He obtained clotting by injecting it into the veins of animals and suggests the importance in human thrombosis of this germ-free product of these bacteria. He noted that the clotting times of the citrated bloods of different animals varied widely, rabbit blood taking 1 to 2 hours, while other animal bloods take as long as 24 hours. The variation in human blood of from 1 to 2 hours to no clotting at all suggested an antibody which he thought might play a rôle in preventing thrombosis. The presence of this antibody in sera with a high antitoxic content and its development in rabbits after prolonged treatment with filtrates containing coagulase supported his contention. Sudhues and Schimrigh searched for the presence of an antistaphylocoagulase in the plasmas of normal persons and in those with staphylococcus infection of many grades of severity as well as in the plasmas of experimentally infected animals. They were unable to find any deviation



from the average of the normal clotting time of citrated plasma by the staphylococcus in any of these, not even in cases in which antistaphylo-lysin was demonstrably present, and suggest that the differences are due to some chemicophysical change in the blood and not due to any coagulase inhibiting antibody. Dolman<sup>3</sup> was also unable to demonstrate this *in vitro* inhibition by antitoxic serum.

**Hemolysin.** According to Gross, hemolysin and leukocidin appear later in cultures than coagulase. Hemolysin does not act the same on the red blood cells of different species. He reported that rabbit blood was most sensitive, bovine less, sheep and goat much less and human, equine and guinea pig blood gave no hemolysis. Dolman<sup>1</sup> found almost the same order of susceptibility, the hemolytic units for a certain toxin being as follows: Rabbit, 8000; sheep, 1600; cow, 200; guinea pig, 40; human, 20; cat, 10; horse, 10. It has been generally agreed that the rabbit is the most sensitive animal for the study of all these toxic substances, and tests against rabbit red cells are useful for titrating the toxic preparations (Gross<sup>3</sup> and many others). It is, of course, clear that the effects of toxins of staphylococci in humans cannot be interpreted, directly, as due to hemolysin when the toxins have such low titers against human erythrocytes. Sheep cells, as Dolman says, may be hemolyzed by a toxin which gives no necrosis in the rabbit skin. It would appear from these and many similar reported findings that only in the rabbit can correlated results from the different properties of these filtrates be relied upon. Although the majority of workers believe hemolysin is but one manifestation of a common toxin all do not agree. Gross found hemolysin and leukocidin appeared at the same time in cultures. Panton and Valentine, in a study of 22 strains, concluded that hemolysin and the lethal and necrotic action vary closely together but with no relation to the leukocidin. The strains from acute severe infections usually develop strong leukocidin and weak hemolysin and just the reverse occurs in strains from long-standing sycotic types of infection. In an annotation in the *Lancet* (2, 261, 1934), covering a criticism of Dolman's<sup>3</sup> reports on the results of serum treatment, it is pointed out that an antiserum should be tested for its power to neutralize leukocidin, for the above reasons. Weld and Gunther, on the other hand, being able to absorb  $\frac{9}{10}$  of the hemolysin and leukocidin of their filtrate on red cells or to completely remove leukocidin by leukocytes, leaving the necrotoxin undiminished, concluded the two were different. Burnet and Freeman state that all the work of their laboratories since 1928 leads to the view that all the manifestations of the toxin produced from their standard toxicogenic strain (white staphylococcus variant S6) on the cells and tissues of rabbits are due to a single toxin. They suggest that the previous workers may have had a toxin with an altered toxophore group, like a preparation of a slowly formaldehyde detoxicated "intermediate" toxin of theirs, with antigenic identity but similar differences in the hemolytic and necrotic tests. Burky<sup>1</sup> reported that the invasive, virulent and pathogenic properties are independent of hemolytic and pigment-producing properties and showed that under anaërobic conditions pigment and hemolysin are practically zero without any impairment of the lethal effect, and in a synthetic medium the production of hemolysin is inhibited with no corresponding loss in the lethal factor. Further, his strain (Ha) at first produced moderate amounts of hemolysin and lethal factor, but on later subcultures the hemolysin was lost and

the lethal factor increased and he even suggests that hemolytic activity inhibits the action of the lethal factor. The hemolysin he found to be unstable, while the lethal factor maintains its toxicity for as long as 1 year without refrigeration. Nélis *et al.* state that the rule, the more lysin the more toxin, is not strictly true. He showed that his medium inhibits the action of hemolysin in the more concentrated doses of the filtrate but the hemolysin is attached to the red cells which lyse immediately on removal from the medium. From such evidence as the above it is clear that titration for the hemolysin content of a filtrate may not be correlated with other properties. Chapman *et al.* include hemolytic tests, using rabbit blood agar, as a valuable measure for the identification of pathogenic staphylococci, but they emphasize that coagulase and pigment production also must be determined to make possible a high degree of precision. Antihemolysin is widely used as an index of antitoxic content of artificially and naturally produced antisera (Gross,<sup>1</sup> and Connor and McKie<sup>1</sup>). Certainly with many of the strains of staphylococcus used for inducing immunity in man and animals it serves as a valuable procedure; but realizing the relatively inert action of the hemolysins produced *in vitro* for human red cells, one wonders whether the artificial antibody content so determined actually indicates a real immunity in the treated human being. Dolman<sup>3</sup> considers the antihemolytic power of antiserum for human therapy as probably of secondary importance from the clinical standpoint.

**Leukocidin.** This product of staphylococcus growth has been incidentally discussed above, but because the purulent character of staphylococcal infections provides a sharp differentiation from many other infections by known toxin producers, such as in diphtheria and tetanus, it should be considered of prime importance in the study of staphylococcus infections. Most investigators have stressed its significance but, largely for technical reasons, it has not recently been systematically studied although such a study is full of promise. Menkin<sup>2</sup> thought a leukocidin-like substance might be responsible for the irritating effect determining localization by fibrin deposition in the lymphatics, although the Reviewer would suggest the probability that the factor is more of the nature of staphylocoagulase, although the latter is heat stable. Panton and Valentine consider leukocidin as different from both hemolysin and the necrotoxin. The fact that antitoxic immunity rarely protects against the living bacteria in experimental animals and from the evidence of high antitoxin content in infected patients (antihemolysin), presumably also in man, this opens up the problem of a more basic explanation for the purulent character of these infections. Although phagocytosis is almost universally accepted as the chief fundamental defense against these cocci, the idea has been advanced that the proteolytic action of an excess number of leukocytes may be a contributory or even a prime factor in the development of the purulent lesions. There is a possibility that materials from the leukocytes may be absorbed by the peripheral nerves and interfere with the normal reflex control of the infected tissue. Benians discusses the problem of pus in infection. If a patient survives the first few days of a pyemia, he emphasizes, the outlook is related to the condition of pus formation rather than to the actual toxic virulence of the infecting agent. He quotes Wright as saying that normal blood contains phagocytes "far in excess of any conceivable requirements." In a series of 4 cases of severe osteomyeli-

tis he gave benzol by mouth to reduce the leukocytosis with good results and based this treatment on the following: Patients quite often die from the violence of their reactions rather than from the virulence of the infections; it seemed as logical to attempt to check hyperleukocytosis as to check hyperpyrexia; leukocytosis increases as immunity develops, and with the neutralization of the toxins the pyogenic capacity of an infecting organism is apt to increase; leukopenia is the result of toxin alone; and he believed leukocytosis and localization of pus is an index rather than a necessary adjunct of immunity. He hopes that a more direct method may be discovered for this purpose. The Fs type of *Staphylococcus aureus* described by Burky,<sup>1</sup> with low toxicity and marked pyogenic characters, supports Benians' hypothesis as does also Gross,<sup>4</sup> who found his less toxic strains were derived from osteomyelitis cases. Schattenberg and Harris studied the effect upon animal leukocytes of a *Staphylococcus aureus* culture from a case of "agranulocytic angina." Suspensions injected into the subcutaneous tissue, the peritoneum, the peritonsillar structures, on and in the scarified tracheal mucosa and into subcutaneous agar, caused neutrophilic leukocytosis or no cell reduction. Filtrates acted similarly. However, the exudate following intraperitoneal injections of guinea pigs, when filtered and injected intracardially and intraperitoneally into animals, produced a granulocytopenia. Pike described a phagocytic depressing effect of filtrates of staphylococci quite independent of their hemolysin or toxic characters. The depression effect is not antigenic, is thermostable, does not deteriorate on standing (4 weeks), is unaffected by an atmosphere of CO<sub>2</sub> and, a similar substance being formed by *Escherichia coli*, it is not specific for staphylococcus. He concluded from this and the early report of Van de Velde, in 1894, that leukocidin is not the cause of virulence.

**Necrotoxin.** The presence of this substance in a filtrate is discovered by its power to produce necrosis in the skin of rabbits. Gross found it appeared only in older cultures (later than hemolysin and leukocidin) along with the lethal toxin and showed it can be preserved in the dry state. In its lability to heat it resembles hemolysin. The test for necrotoxin is not easy to standardize. Dolman<sup>1</sup> used as the criterion an edematous white or yellow patch on the second or third day with a rim of erythema, but if a scab or necrosis is demanded then the titer is much lower. Nélis *et al.* required a scar. Gross<sup>4</sup> divided his strains into three groups by the type of reaction as giving (1) necrosis, (2) red infiltration and (3) negative reactions. Burky<sup>2</sup> particularly showed how important the breed of rabbit was for the type of skin reaction and described similar kinds of reactions with his three types of organisms and indicated that the sensitivity to the barium sulphid depilatory foretold what the reaction would be to filtrates. Another source of confusion is the marked differences in the "normal" antitoxin in rabbits and this should always be tested as antinecrotic rather than antihemolytic (which is rarely done) before the animal is used for the test. Burky<sup>3</sup> further showed that age was of great significance in that young rabbits under 4 months were non-reactive to the cutaneous injection nor can they be killed even by large intravenous injection. This is not due to an immunity but suggests to him that the reaction is of an allergic type. Kobak and Pilot had previously noted the same phenomenon in humans, using vaccines and filtrates, finding that newborn babies failed to react when the mothers did and that this

reactivity gradually developed with age. Dolman<sup>1</sup> found older guinea pigs were relatively more susceptible to the lethal effects of filtrates than were younger ones. Connor and McKie<sup>1</sup> suggest that the antitoxin effects after toxoid treatment may be due to desensitization. Panton, Valentine and Dix induced immunity by intradermal injection of staphylococci and found antibodies present in his animals in that a smaller lesion followed an injection, but there was also an increased sensitivity in that lesions were produced with a much smaller dose. They consider this latter phenomenon as a factor in the relapsing infections as they occur in man. They tested toxin intradermally in humans and obtained strong reactions in those with a history of recent infections and in those with small lesions (boils and sycosis) but severe cases usually gave negative reactions. They also compared this to the allergic phenomena in tuberculosis. Julianelle and Wieghard obtained from staphylococci two type-specific carbohydrates: Type A from virulent pyogenic strains, the other, Type B, from non-pathogenic strains. Two convalescent patients gave skin reactions to 0.1 cc. of a 1 to 50,000 dilution of Type A carbohydrate but not to Type B.

**Lethal Toxin.** The lethal effects of filtrates are the most dramatic of all toxic manifestations. With strong toxins there is practically no incubation period after intravenous injections and death is very rapid. This toxin is, therefore, different from the other commonly studied toxins such as diphtheria and tetanus and does not seem to be primarily a neurotoxin, although many include parts of the nervous system as affected in its general toxic action. The macroscopic lesions may be few, but if death is delayed for a few hours a serous pericarditis is noted (Nélis *et al.*) or sometimes a peritoneal exudate or hemorrhages in mediastinum, kidney and other organs. The microscopic study indicates a profound destruction of red blood cells in the veins, a lysis of the protoplasm of liver cells and other similar but less regular changes in other parts. These workers believe that death in acute cases is due to cardiac deficiency of sinus origin and in delayed death to functional deficiency in many organs as the liver, kidney and lungs. Antitoxin inhibits these effects. Burky<sup>1</sup> found that one type of coccus (strain Ha) kills in this general way, the other (Fs) kills after producing multiple abscesses. There is scarcely space to consider in further detail this lethal poison, but it should be emphasized that by analogy similar pure toxic deaths are considered as possible in man. If they do occur, it is only on very rare occasions and the human problem is much more often a pyogenic one. Practically all investigators have reported that there is no correlation between the degree of toxin production *in vitro* and the severity of the infection induced in the human by a given strain.

**Antitoxin.** It is rational to use antitoxin for cases in which the immunology is quite clear and, indeed, antitoxin is being rather widely tested. In animals, although clean-cut results have been obtained in toxin-antitoxin experiments, there is a great deal yet to be learned about its mode of action and the effects of it in humans. Medical history is filled with laboratory experiments which have not fulfilled expectations in the clinic. The protection against injections of living virulent cocci is difficult to obtain. Connor and McKie<sup>2</sup> were only successful in immunizing 3 of 11 rabbits against injections of living cocci by the use of living subcutaneous vaccines followed by toxoid. Parish, O'Meara and Clark have been successful in immunizing rabbits with toxoid against intracutaneous and very occasionally against many

lethal doses of virulent cocci intravenously, but passive immunity against virulent cultures usually only delayed death. Burky<sup>2</sup> found two types of immunity according to the kind of rabbit used: one is an antitoxic immunity, rather permanent, in rabbits not readily growing hair after depilation and produced by his toxic strain (Ha); the other is a kind of desensitization immunity by all filtrates and is only temporary. Winzeler gave living virulent cultures to guinea pigs by dropping in the throat from a syringe, with starvation before and after, and succeeded after 3 to 4 weeks in protecting 17 of 25 against three times the fatal subcutaneous dose.

The results of the use of antitoxin in the human is difficult to evaluate because of the lack of reliable statistics and the very wide variation in the reaction of human beings at different ages and under different conditions to staphylococcus infections. Patients with apparently the most severe kind of infections often recover, so that it is wise to be ultra-cautious in interpreting results. As an example, the report by Nesbit of 48 cases of acute staphylococcal infections of the kidney apparently of hematogenous origin can bear careful consideration. These patients have a stormy first week followed by a gradual improvement, so that a normal temperature and no pain is the rule by the fourteenth day and without surgical interference. Uncomplicated cases end in complete recovery and none become chronic. He had only 4 (8.3%) with perinephric abscess requiring operation. Even primary staphylococcic pneumonia is not always as fatal as is generally supposed. Reimann lost only 2 of 6 such cases. The blood cultures remained negative in all. Pantón, Valentine and Dix, in discussing the difficulties in assessing results after antitoxin treatment, say that in the ordinary case of acute osteomyelitis before exposing the bone blood cultures are positive in about 90% but that this is not prognostically bad. Pyrah and Pain had a mortality rate of 27.1% among 262 consecutive cases of osteomyelitis in which operations were done. Gross considered antitoxic serum should only be used for cases with septicotoxic symptoms, for severe cases of osteomyelitis, carbuncles on face and neck and those where toxin absorption is definitely present. In 1934,<sup>4</sup> he discussed the bases for serum therapy in osteomyelitis, indicating that the defenses here are phagocytic leukocytes and antitoxin. The serum from such cases should be tested for antihemolytic, antinecrotic and antilethal action. He recommends the use of serum from osteomyelitis convalescents with high antitoxin content and if the serum of horses is to be used the strains of Group II staphylococci, with lessened hemolytic and lessened necrotoxic characters should be used for immunizing. Pantón, Valentine and Dix treated 13 cases, carefully chosen for their severity, with antiserum containing antileukocidin given intramuscularly in all but 1. The results in 5 cases with severe carbuncles were indefinite, the first 2 were benefited, the last 3 not, but 1 of these was truly hopeless. All 5 cases of septicemia and pyemia recovered, a striking result being obtained in 1 case of osteomyelitis; but there never was a dramatic fall in temperature and pulse rate. Three fulminating cases died. They believed the serum therapy prevented death in some and shortened the course in all. The most extensive use of antitoxic serum is given in a paper by Dolman<sup>3</sup> in which he reported 104 cases so treated. The intravenous route was used in most of the cases "and usually occasioned a severe reaction" with "rigors," sometimes almost "delirium and then circulatory collapse and hyperthermia." Burky,<sup>5</sup> in his study on rab-

bits treated with immune serums, says "certain serums, supposedly immune and with high precipitin titers, seem to increase the lethal action of the toxin." Dolman, because "a number who eventually died . . . lived several days longer than was at first anticipated" and because "a few hours after—some—showed a remarkable improvement," did not seem to be impressed by the probable danger of such reactions on the kidney, heart or other organs. His general results show that 62.5% recovered. All but 2 of these patients were treated in hospital. If we leave out the 24 cutaneous and subcutaneous cases, none of whom died, the recovery rate is 51.25%. The group of 32 cases of staphylococcemia in children secondary to osteomyelitis, which he particularly stresses, showed a recovery rate of nearly 69%, and the balance of 48 cases showed nearly 39.6% recovery. Accepting that children are somewhat less sensitive to staphylococcus infection, that bacteriemia in osteomyelitis cases (see above) may not be prognostically bad, and that in the series of osteomyelitis cases reported by Pyrah and Pain the recovery rate was 72.9%, it would appear that the use of antitoxin serum in the general run of infections is scarcely encouraging. In the group with staphylococcemia, leaving out those secondary to osteomyelitis in children, the recovery rate is about 22%. An annotation on the above report (*Lancet*, 2, 26, 1934) says that "the striking difference between the mortality in these 'negative (blood) culture' cases (4 deaths among 40) and in the 'positive' (35 among 64) shows that staphylococcal antitoxin cannot be expected to work miracles in face of an established septicaemia with multiple metastatic abscesses." The difficulty in forming a definite estimate of the effect of antitoxin in such pyogenic infections is pointed out and "since no satisfactory controls can be provided, one has to rely mainly on clinical evidence of improvement" which accompanied by an increase in the antitoxin content of the patient's serum occurred in this series and indicated "that antitoxin is of real value." It is clear how extremely hard it is to draw conclusions in this matter. Even in such highly fatal infections as those of the brain and meninges, in which 4 of 6 cases recovered, each case must be considered on its merits. One of the recovered cases of meningitis had received active bacteriophage with no immediate results, but since at least 3 cures of meningitis have been attributed to bacteriophage (for reference see Eaton and Bayne-Jones), and that other immunologic effects besides direct lysis have been suggested in bacteriophage therapy, its bearing on this case cannot be summarily dismissed. The second case of meningitis seems to have been definitely benefited and recovered following intracisternal and intramuscular injections. The third case died. Of the 3 cases of brain abscess, 1 had been treated with toxoid previously and at and after operation with antitoxin and would undoubtedly have recovered but for the erysipelas and the resulting streptococcus meningitis; the other 2 cases recovered after drainage, the antitoxin being used to prevent meningeal involvement. Two other fatal cases secondary to staphylococcemia are also recorded under another heading. Antitoxin has certainly not fulfilled our expectations.

**Toxoid.** The fact that toxoid preparations could readily be made from staphylococcus toxins has helped greatly in the study of the subject. However, we need not review the details of its production and use in obtaining antitoxin in animals. It is generally agreed that the fundamental antigenic characteristics distinguishing the crude or

purified toxins are more or less retained after formaldehyde treatment. Its use for inducing antitoxin in man is receiving much attention. From what has been said, the limitations of pure antitoxic immunity for the complicated problems of these pyogenic bacteria with their multiple biologic qualities will, we hope, have been made evident. It seems a perfectly logical procedure to build up antitoxin as a defense mechanism if it is reasonably certain that no abnormal or harmful sensitization will later result. The use of vaccines with killed cocci has had a long and variable history of great successes and as many failures. The problem should be restudied with the newer knowledge available and careful comparative and combined results thoroughly analyzed. Barber and Forman tested vaccines intradermally in sycoses, the most difficult of all infections to cure. He obtained 9 complete cures after prolonged treatment with graded increasing doses, 3 almost complete and 1 with the sycosis cured but a blepharitis remaining. These cures were more permanent than by other methods. Connor and McKie<sup>2</sup> treated 18 cases of sycoses—because of the comparative rarity of spontaneous or any cure—with toxoid, with cure in 10 and in 4 with a few pustules still appearing each week in spite of the presence of a high antitoxin in the blood. Nineteen other superficial infections gave equally good results. Dolman<sup>2</sup> successfully treated with a pooled toxoid 28 patients with intractable staphylococcus infections (16 with severe boils, 6 with pustular acne, 1 case each with acute bullous impetigo, recurrent eczema, severe pustular dermatitis, extensive cellulitis after laparotomy and 2 of sinusitis). Antitoxin (antihemolysin?) developed in all and the doses varied from 2 to 20. He concludes that "cases of recurrent and persistent boils, in my experience, invariably respond to toxoid treatment."

Kindel and Costello tested a commercial toxoid made from a potent necrotizing toxin on 42 cases (acne vulgaris, 28; furunculosis, 6; sycosis vulgaris, 8). The acne cases, because due to a combined infection, are not as useful for the purpose as are pure infections. Of the 8 cases of sycosis, 4 were unimproved by the treatment and 4 were worse; of the 6 cases of furunculosis, 3 were improved and 3 were worse. This report, which cautioned against becoming overenthusiastic about the method, resulted in a letter of protest from Dolman,<sup>4</sup> who rightly emphasized certain important features of the toxoid he had used. Cornbleet and Rattner supported the views of Kindel and Costello, having had unsatisfactory results with sycosis barbæ and good results in only 2 of 4 cases of furunculosis, in 1 of which a relapse followed, while 1 man developed a huge carbuncle on the thigh after an "adequate" number of injections of toxoid in the arm. Sharlet suggests that Dolman had not appreciated the toxoid situation in the United States, where the products from manufacturers of biologics are often tested and endorsed under relatively unfavorable conditions. Parish, O'Meara and Clark treated patients with superficial boils and pustular acne with toxoid and say that "a few have ascribed the rapid disappearance of their boils to the injections of toxoid," and all showed an increase in antitoxin titer. Gilchrist and Wilson being impressed with the high incidence in their diabetic patients of staphylococcal infections in the upper respiratory tract, and believing that the staphylococcus toxin increases the metabolic rate and is, therefore, detrimental to the patient, used toxoid with most satisfactory results. The dose of insulin could be reduced and the improvement continued in spite of

adverse weather conditions. It may be of interest that Danbolt, in studying the epidemiology of furunculosis, concluded that the frequent finding of similar types of cocci in the nose and in the furuncles indicated that this nasal infection might play a rôle. Neither bacteriophage nor vaccines had any effect on the nasal staphylococci.

**Bacteriophage.** The belief that bacteriophage was of marked value in the treatment of staphylococcus infections was shaken when it was shown that blood and tissue fluids inhibited the action of phage. Mutsaers, in 1931, showed that the bacteriophage becomes fixed on staphylococci living or dead and that normal serum prevents this fixation but does not destroy the phage even after a month's contact. He did not find that serum inhibited the action of phage on *Staphylococcus albus* nor did it affect the absorption. He compares this result with the coagulase action of *Staphylococcus aureus* and its absence in *Staphylococcus albus*. d'Herelle and Rakieten claimed that hemolytic staphylococci (tested on rabbit, guinea pig or human blood agar) are particularly susceptible to bacteriophagy and resistant strains are generally of the non-hemolytic type. This has not been the opinion of many and susceptibility does not seem to follow any rule. Every staphylococcus, whatever its other characteristics, must be tested to determine its susceptibility. McKinley calls attention to the fact that at least 39 hemolytic strains have been studied which are resistant to bacteriophagy. Jern, Howes and Meleney found only 8 among their 110 freshly isolated strains were resistant to bacteriophage. They demonstrated that phage instilled into the cutaneous lesions did not increase, but persisted there for a day or more and only gradually became weakened. Although the disappearance of cocci was negligible, there seemed some correlation between this persistence and the apparently marked benefit from the treatment; but there was no correlation between persistence of phage and the presence of so-called "antiphage" in the patients' serum. The changes noted in the cocci after phage treatment were towards loss of virulence which occurred frequently in the test tube but less often in the lesions. Wollman and Wollman studied the secondary lysis of dead staphylococci in the presence of phage and showed that in sealed tubes this occurs only when living susceptible staphylococci are added with the phage, the same phenomenon occurring when resistant living strains of the same type are used in place of the dead cocci. This lysis is not transmissible. There are certain products (diastases?) set free in the bacteriophagic process which accounts for the action. They suggest this as a method for obtaining lysates of refractory staphylococci. Whether such an occurrence can take place *in vivo* is not discussed. Rakieten reported on this same subject. He found that the lysis of a resistant strain occurs under the action of the bacteriophage lysin when it is in contact with the regenerating phage. He refers to bacteriophages which are not inhibited in whole blood or pure serum, also to strains of non-hemolytic staphylococci which absorb large quantities of some polyvalent bacteriophages and destroy others. The real reason for the inhibiting action of body fluids under artificial conditions he considers as yet unknown. Burky<sup>4</sup> studied the inhibiting action of animal sera and purulent exudates which he confirmed. His type strain of toxic staphylococcus Ha is very resistant to bacteriophage, while strain Fs, a pyogenic type, is sensitive. Immune serum does not inhibit the action of bacteriophage on the Fs type, and this suggested that antitoxin might enhance the effectiveness of



bacteriophage in infections produced by this F<sub>s</sub> type (osteomyelitis and other purulent lesions) which in itself produces no toxin and hence no antitoxin can be formed in the patient. He believes the failure of bacteriophage in the tissues is due to the increased resistance of the Ha type. Larkum discussed the suggestion of d'Herelle, that bacteriophage was an antitoxin. Toxin and antitoxin are now well known and he has studied how they are related to bacteriophage. Bacteriophage is not hemolytic for rabbits' red cells; it did not inhibit the hemolytic action of toxin but, injected purified or unpurified into rabbits, it produced sera which were antihemolytic and antinecrotic. He, therefore, concluded that bacteriophage is neither toxin nor antitoxin but is apparently of the nature of a toxoid. The importance of these findings in the therapeutic use of staphylococcus is emphasized in another article. Schultz and Gebhardt, having been successful in curing a series of horses suffering from boils as well as getting benefit in a variety of infections in man by the use of bacteriophage lysates, consider that these are more potent antigens than are vaccines. MacNeal *et al.* bring experimental evidence that the mechanism of bacteriophage action in experimental staphylococcus bacteremia is the stimulation of endothelial phagocytosis, the restraint of growth of those cocci which have lodged in the internal organs and a favoring action on intracellular digestion. The therapeutic applications of bacteriophage in general have been fully reviewed by Eaton and Bayne-Jones, in which staphylococcus bacteriophage is carefully considered. They emphasize the frequent lack of critical analyses by the advocates of this therapy, but conclude that "staphylococcus infections in general appear to have responded the best to bacteriophage therapy." Bacteriophage cannot therefore be dropped from the list of things to be studied in any real approach to the solution of the problems of staphylococcus infection.

**Food Poisoning.** A word may be added about a few of the more recent developments in the problems of staphylococcus food poisoning. Only certain species of monkeys, and man irregularly, have been found to be sensitive to the ingestion of the toxic substance. Borthwick, however, has been able to bring about death in the guinea pig and the rabbit, in from 2 minutes to 5 days, by putting the toxin from toxigenic strains of *Staphylococcus aureus* (from a carbuncle and also Burnet's strain) into their stomachs after the acid contents had been reduced to a pH value near to 7.3. This observation, if confirmed, may lead to a better explanation of these outbreaks. Dolman<sup>5</sup> was unable to obtain any effects when various filtrates containing potent exotoxin were consumed in milk or water by 42 volunteers on 110 occasions and at various times before and after meals. A filtrate, however, from a strain of the food poisoning type received from Jordan caused severe gastro-intestinal disturbances in 3, and to a lesser degree in 4 of 9 volunteers, and in 1 person after the exotoxin had been fully neutralized with antitoxin. This strain, originally isolated from an abscess in a human, gave white colonies (later becoming pale cream colored) and hemolysis on sheep blood agar. It produced no exotoxin when grown in broth in air after 60 hours nor had it any effect on 5 volunteers who drank it. However, when grown in 0.3% agar in CO<sub>2</sub> it yielded a filtrate giving reactions for both toxic factors, killing a rabbit and producing symptoms in man as recorded. He believed the substance responsible is distinct from the exotoxin, is only produced by an occasional strain

under very special conditions and that the actual incidence of staphylococcal food poisoning is, therefore, not likely to be high. Crabtree and Litterer report a series of severe outbreaks of milk poisoning, with 242 cases among 97 people at a farm school in a period of 50 days. The responsible organism (*Staphylococcus aureus*) was traced to 2 cows from a herd of 13. It would appear from their study that the staphylococcus had opportunities to grow in the milk stored in large cream cans and under these conditions had produced the poisonous substance, but whether these conditions simulated those postulated as necessary by Dolman is not altogether clear. A more complete study of the toxin of these particular strains will be awaited with interest.

The progress during the last few years has greatly increased the knowledge of the mode of infection and wide potential powers of the staphylococci and there is a hope that more scientific methods of treatment and prevention may develop if all the various aspects of the problem can be properly correlated and effectively evaluated. It is a difficult subject with many aspects not touched upon in this review, such as the influence of diets, trauma, the age incidence and the therapeutic effect of local rest. Such a discussion as Hallam has given on recurrent boils, in which toxin is not mentioned and vaccines are perhaps underestimated, merits reading. He emphasizes that more fatalities come from furunculosis than from any other skin disease.

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## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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## EPIDEMIC ENCEPHALITIS.

WITH SPECIAL REFERENCE TO THE ST. LOUIS OUTBREAK OF 1933.

THE occurrence of the first important outbreak of epidemic encephalitis in the United States in St. Louis, Mo., during the summer of 1933, has aroused interest in the study of this disease or group of diseases, depending on whether one considers the various clinical entities as due to one or more than one etiologic agent.

Practically all workers in this field are in general agreement that a virus is the cause of the various clinical conditions encountered. Apparently the only exception is Rosenow, of the Mayo Foundation, who found streptococcus in a goodly proportion of the St. Louis cases, having isolated the organism either from the blood stream or from the upper respiratory passages. Weil found cocci in the central nervous system of fatal cases but, though suggesting that they should not be dismissed lightly, did not express any opinion as to their significance.

Three types are generally recognized, based on clinical, pathologic and epidemiologic grounds: (1) Lethargic encephalitis of von Economo, sometimes spoken of as the "winter" type, or Type A. As one of the synonyms indicates, the onset appears to be more frequent in the winter than in the hot months of the year. (2) The postinfectious type sometimes seen after measles, whooping cough and other infectious diseases, but chiefly studied in recent years as a sequel to vaccinia. (3) The epidemic type, which is regarded as the type that prevailed in St. Louis. This type has prevailed in Japan since approximately 1871. It is usually designated as the B, or Japanese, type. Neal, after studying the St. Louis outbreak, considered it probable that these various types are manifestations of the infection by one virus. Neal later expresses the view that more than one virus is concerned in the causation of acute epidemic encephalitis. Her classification would make two types from the clinical-pathologic point of view: (a) Meningoencephalitic type, and (b) encephalomyelitic type.

To illustrate the difficulty in classifying these central nervous system manifestations of various diseases it may be noted that Neal regards the Australian outbreak of 1917-18, usually designated as "X" disease, as probably epidemic encephalitis, while Flexner, on the basis of pathologic findings, regards it as more suggestive of poliomyelitis. Possibly, as Neal suggests, both encephalitis and poliomyelitis were present in the outbreak of "X" disease. The clinical symptoms did not fit either in a satisfactory manner.

Rivers is unwilling to express any final opinion on the identity or non-identity of the virus in the different epidemics. He calls attention to the fact that the same neurotropic virus may give very different clinical pictures and refers to a comparatively recent outbreak of rabies in the Island of Trinidad where the clinical picture was that of Landry's paralysis.

Leake, of the Public Health Service, who perhaps devoted more study to the St. Louis epidemic than any other one person, is disposed to regard the virus then prevailing as separate from the one which probably gives rise to the other types of encephalitis.

Webster and Fite, on the basis of serum neutralization tests, indicate that the Japanese B virus is different from the St. Louis virus.

Wooley and Armstrong, from their serum-virus neutralization tests, are disposed to consider the St. Louis virus as an entity different from the virus causing the other types of encephalitis, and practically proved it to be different from the virus of the A type, the virus of postinfectious encephalitis and the virus of poliomyelitis.

Brodie found the serums from cases of chronic encephalitis showing Parkinson syndrome (presumably endemic encephalitis of the von

Economo or A type) devoid of virus neutralizing antibodies for the St. Louis strain.

If anything were needed to complicate the picture of confusion, it is to be found in the fact that Armstrong and Lillie have isolated from one of the St. Louis cases a virus which, in its behavior in animals and production of pathologic appearances, differs from the other viruses isolated in the same outbreak.

Finally, Weil, on the basis of von Economo's studies and his own experience (the latter in the field of pathology), feels that neither clinician nor epidemiologist is in position to decide as to the identity or non-identity of the St. Louis epidemic with other epidemics. Several workers have succeeded in establishing and maintaining strains of the St. Louis virus in monkeys and mice; other laboratory animals appear to be insusceptible.

The clinical features are important in establishing the type of the infection prevailing. The incubation period may be anywhere from a minimum of 4 days to a maximum of 21 days, usually being from 9 to 14 days. The characteristic symptoms as manifested in the St. Louis outbreak were sudden onset, high fever ( $104^{\circ}$  to  $105^{\circ}$  F.), headache, stiff neck, nausea, disorientation, tremors, abolition of abdominal reflexes. Drowsiness was common, but coma was rare. The leukocyte count was either low, normal or elevated. The spinal fluid was found to be clear in the majority of cases under moderate pressure and carrying cells from 100 to 300, lymphocytes predominating. In 7% of the cases, however, the spinal fluids presented no cellular abnormality. The first spinal fluid may be normal while a subsequent one shows characteristic changes. Spinal fluid sugar, according to Barr, is well above the range seen in tuberculous meningitis. There were few cases, or none, with disturbances of the ocular muscles such as are so common in the von Economo type of the infection.

The Parkinson syndrome, mental changes and other indications of grave disturbance of the central nervous system so common after attacks of endemic encephalitis were conspicuous by their absence after recovery from the St. Louis type. From the clinical point of view, the relative absence of sequelæ is perhaps the most striking difference between what we would prefer to call the epidemic type of encephalitis and the endemic type (von Economo or A type).

McFadden, on the other hand, found a few evidences of residual nerve system damage in some patients at the time of discharge from the hospital and suggests that time may show serious sequelæ.

The death rate was approximately 20%, but when recovery occurred it was prompt. Kinsella and Broun say the average patient was well in 10 days, but they also note that minor disabilities were not unusual. They agree with other observers, however, that the serious sequelæ so common after the lethargic type did not follow attacks of the St. Louis type of the disease.

Most observers note that there were mild cases, cases which surely would not have been recognized in the absence of an epidemic.

Eschenbrenner reports that no special therapeutic agent appeared to be of value in treatment; even convalescent serum appeared to be of little value; Finnigan thought antistreptococcus serum of value. Neal urges that hospitals especially designed for encephalitis patients should

be provided in the interest of patients, their families and the furthering of treatment and research.

The epidemiologic features of the outbreak were of special interest. There was a total of over 1000 cases reported. The earliest came from the suburban areas of St. Louis early in the month of July, and it was not until the end of that month that cases began to be recognized in the city proper. Retrospective diagnoses then and later indicated that some cases even earlier had been missed. The epidemic had a direct seasonal prevalence, being confined to the hot part of the year. This agrees with the experience in Japan where hot, dry seasons are prone to be associated with outbreaks of the disease. An interesting feature was the fact that not only did the outbreak appear to begin in the rural areas but also the highest incidence was not in the crowded part of the city but in the much less densely populated surrounding country. Race and sex appeared to offer no significant differences in incidence. The older age groups (above 35) show a higher attack rate than the younger. Multiple cases in families were very unusual, indicating that the infection is not readily communicable.

The exact mode of spread remains to be determined. It has been customary to say that it was similar to the spread of poliomyelitis, but this, in reality, is not advancing one's acquaintance with the subject very extensively. It is interesting to note that cases originating from infection in St. Louis, which developed the disease elsewhere, did not result in any material spread of the disease in other communities though a few neighboring cities had a modest number of cases; whether or not these originated from cases infected in St. Louis could not be determined.

Early in the epidemic, mosquitoes came under suspicion as possible vectors but these, together with food and water, were excluded. Studies by Wooley and Armstrong on the distribution of the virus of endemic encephalitis in the United States indicate that, on the basis of serum-virus neutralization tests, the infecting agent appears to be much more widely distributed than had been suspected. They found that serum of about 95% of recovered cases neutralized virus while serum from 35.7% of contacts of clinical cases neutralized the virus, and 9.4% of normal non-exposed persons yielded serum which gave neutralization.

Geographically, they found a very wide distribution of individuals whose serum would neutralize the St. Louis virus. This finding raises the question as to why epidemics are so rare when the virus appears to be so widely distributed.

With respect to control measures, it is obvious that little can be said in view of our lack of knowledge of the means of transmission. It was customary in St. Louis to hospitalize patients as far as possible for two reasons: (1) To effect isolation, and (2) for better opportunity for early diagnosis. This isolation was maintained for 3 weeks from onset. Schools were kept open. Bredeck, Commissioner of Health, St. Louis, whose opinion is entitled to the greatest weight, has the following to say with respect to the public health aspects of the disease:

"That the measures of early diagnosis, hospitalization and isolation were efficient can be measured only by the fact that 95% of the reported cases were hospitalized. How successful in checking the disease this was is a matter of speculation. There is no actual method that we

can apply in determining the efficiency of such measures. They are, however, those that have been recognized in the handling of all communicable diseases. Our greatest consolation was in the fact that we did not issue regulations which were not based on sound public health practice. Until more fundamental knowledge is forthcoming concerning the true etiology, mode of spread, or specific remedies for this disease nothing could be advocated further."

G. W. McCoy, M.D.

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 21, 1935.

**The Excretion of Reducing Materials in the Urine of the Normal Dog.** EDWIN P. LAUG (Laboratories of Physiology, University of Tennessee and University of Pennsylvania). The estimation of carbohydrates in bread by *in vitro* and *in vivo* (phlorhizin) methods reveals only their gross availability, without distinguishing more subtle modifications resulting from heat treatment. By using a sensitive method for detecting reducing materials in specially prepared urine filtrates, the hourly changes in non-fermentable, fermentable and hydrolyzable fractions in the urine of 2 normal dogs was studied. Feeding various kinds of bread preparations resulted in the following observations:

1. Crust, in contrast to white inside portions of bread, caused a considerable rise in total reducing materials; of this rise, 92% was accounted for by the increase in the non-fermentable fraction.

2. After three different kinds of bread, the response in excretion of reducing materials was lowest with rye, intermediate with wheat and highest with whole-wheat bread.

3. The reducing material revealed by hydrolysis of urine filtrates

was practically 100% fermentable and was not produced at the expense of the non-fermentable material present before hydrolysis. After whole-wheat feeding, however, the hydrolyzable fraction decreased by about 50% and was only 25% fermentable.

**Histamin and Leukocytosis.** V. H. MOON (Laboratory of Pathology, Jefferson Medical College). The discovery of histamin in the various tissues of mammalian animals has led to intensive investigation in attempts to discover its physiologic significance. It appears that histamin performs several functions, some of which are important factors in the inflammatory reaction. Apparently the effect of histamin upon leukocytes in the circulating blood has not been thoroughly studied. Perhaps this is due to an early incidental observation to the effect that histamin produces leukopenia. Attempts to verify this observation have led to results of the opposite character. The intravenous injection of histamin phosphate, in doses ranging from 1 to 2 mg., into cats was followed regularly by leukocytosis. The increase in leukocytes was evident within 15 minutes and continued to a maximum 2 hours following the injury. The leukocyte count remained high for 6 to 8 hours and subsided approximately to normal in 24 hours. Similar results followed the subcutaneous injection of histamin phosphate in monkeys. The increase was chiefly among the polymorphonuclear leukocytes. Injections of saline solution under the same experimental conditions were not followed by significant changes in the leukocytic counts. Differential counts made on cats resulted in the following average leukocytic formula:

Polymorphonuclear leukocytes: Normal, 47; after histamin, 68.

Lymphocytes: Normal, 50; after histamin, 30.

Monocytes: Normal, 3; after histamin, 2.

**A Comparative Study of the Actions of Morphin and Dilaudid (Dihydromorphinone Hydrochlorid) on the Intact Small Intestine of the Dog.** CHARLES M. GRUBER and JOHN T. BRUNDAGE with the occasional assistance of ANTHONY DeNOTE and RAYMOND HEILIGMAN (Laboratory of Pharmacology, Jefferson Medical College). Intestinal activity as influenced by morphin and dilaudid was studied in unanesthetized dogs with Thiry-Vella loops of the jejunum and ileum, using balloons, 30 to 70 mm. long, 20 mm. diameter under a pressure of 15 cm. of water. The drugs were dissolved in Ringer's solution and injected intravenously. The minimal dose of dilaudid causing an increase in general tonus was found to be 0.0002 and 0.0003 mg. per kg., respectively, for the jejunal and ileal loops. The corresponding amounts of morphin were 0.002 and 0.003 mg. per kg. In small and medium doses, dilaudid is ten times more active than morphin in causing an increase in general tonus. Large doses of dilaudid cause a decrease in general tonus of the jejunum and cause less increase in the general tonus of the ileum than do medium doses.

The average rate of the rhythmic contractions of the ileum in the unanesthetized dog is 10.8 contractions per minute, and for the jejunum 13.3 per minute. The effects of morphin and dilaudid upon the rate of the rhythmic contractions are not constant and no conclusions could be drawn.



The effects of these drugs upon the peristaltic activity are also variable; sometimes they cause a disappearance of these movements and at other times these drugs increase their amplitude and rate.

**The Permeability of Living Cells to Heavy Water (Deuterium Oxid).**  
BALDUIN LUCKÉ (Laboratory of Pathology, University of Pennsylvania). The unfertilized egg of the sea urchin, *Arbacia punctulata*, has been used as a cell which allows accurate determination of permeability to water and ready recognition of injury.

It was found that the rate of penetration of heavy water,  $D_2O$ , is the same as that of ordinary water,  $H_2O$ . The physical differences between these two fluids are, therefore, not of sufficient magnitude to effect differences in their rate of cell penetration under the driving force of osmotic pressure.

As has been reported for most other biologic material tested,  $D_2O$  in sufficiently high concentration proved injurious to the test cell. This was indicated by inhibition of development of fertilized cells. However, the similarity in rates of penetration of  $D_2O$  and  $H_2O$  observed in the present experiments may be regarded as evidence that heavy water does not exert its injurious effects through (rapid) changes in cell permeability.

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ORIGINAL ARTICLES.

LOBAR PNEUMONIA AND DIGITALIS.

BY ALFRED E. COHN, M.D.,

AND

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(From the Hospital of the Rockefeller Institute for Medical Research.)

THE question is still undecided whether the action of digitalis benefits patients suffering from lobar pneumonia. This question is, of course, distinct from the one which asks whether giving digitalis to such patients acts at all. To the second question, the evidence permits an affirmative answer.<sup>1</sup> In view of the value which giving digitalis may possess, a decision on the first question is eminently desirable. A solution has not been possible because a simple test is not available. Reliance must still be placed on its average behavior.

The careful and detailed study which was published by Wyckoff, DuBois and Woodruff<sup>2</sup> and by Niles and Wyckoff<sup>3</sup> has focussed attention anew on this problem. The plan of their study offered several advantages: (1) It dealt with relatively large numbers; (2) the duration of the observations was brief; (3) the dose and value of the preparation used was known; (4) an attempt was made, by strict alternation of cases, to solve the problem of control. To complete the investigation in a brief period has presumably this virtue, that the virulence of the infection may be regarded as having remained uniform. And strict alternation of patients has presumably this additional virtue that, provided the number of patients is large enough, the treated and the untreated include in adequate numbers all the varieties of resistance presented by patients. The

method of alternate selection appears to be the method of choice when the number of variable pathologic phenomena is large and their value difficult to assess. The method escapes the embarrassment due to these causes (number and value of phenomena) on the assumption that the cases become distributed equally in two great groups with reference to a selected variable, such as the effect of the action of digitalis. It is the familiar experiment of tossing a penny. The conclusion drawn from this study was "that the routine giving of digitalis to patients with lobar pneumonia is dangerous."<sup>2</sup>

The validity of the method for the purpose of studying the value of giving digitalis in cases of lobar pneumonia may be tested from two points of view; in the Bellevue study:<sup>2,3</sup> (1) Was the virulence of the infection constant, as was supposed to be the case during the brief duration (2 years) of the observation? and (2) Is the reaction of patients sufficiently alike so that they may be treated like the pennies in the experiment?

1. To be certain that the degree of virulence remained uniform is perhaps impossible. The data concerning mortality which are available show that in the Bellevue-Yorkville district (New York City), within which the Bellevue Hospital is situated, in the 5-year period, 1927-1931,<sup>4</sup> the death rate per 100,000 from pneumonia (all forms) varied from 126 (Area 112) to 340 (Area 64). The Bellevue Hospital is located in Area 60 and here the rate was 631. During the same period the rate in Bellevue-Yorkville district was 210; in Manhattan, 169; in New York City, 127. The inference which is drawn is that virulence, reflected in rates of mortality, so far at least as it can be judged by such methods, was not uniform.

2. Susceptibility also varies.<sup>5,6</sup> The risk may conceivably differ if, in patients, three lobes of the lungs are involved rather than one; if the age is over 40; if bacteria are present and persist in the blood; if complications are present; if patients are alcoholic; if they are hard manual workers. Niles and Wyckoff did, in fact, regard sex, age, type of pneumococcus, complications, bacteriemia and auricular flutter in their estimate of the effect of giving digitalis. But comparing treated and untreated cases from the point of view of these disadvantages, one at a time, fails to take into account the risk which a given individual runs. He is not of a certain age nor suffering, one at a time, from bacteriemia, from complications or cardiac arrhythmia. He is, as a matter of fact, a person whose chances of recovery may depend precisely on the variety and on the number of these or other untoward factors of which he is the subject. But judgment should be delayed until it is demonstrated that the issue depends on what might be called "the severity of the disease." Niles and Wyckoff take this consideration into account in 1 instance in which they combine two factors, age and type of pneumococcus (Table 6).<sup>3</sup>

Because of the difficulties involved in the method of alternating cases, the analysis now reported was undertaken from the point of view of the principle of "severity of disease."<sup>5,6,7</sup> At the basis of this principle is the idea that patients suffering from lobar pneumonia encounter risks far from uniform. The risk varies, presumably, with the kind and number of factors of an untoward nature which each case presents. These are being called "untoward," "unfavorable," "disadvantageous" factors or phenomena or elements. Eight such factors have been singled out for study. Still other ones might have been chosen.<sup>5</sup> Obviously from this point of view the analogue of the experiment with a two-sided penny requires extension. As many such experiments must be carried on as there are groups of patients. Since there were 146 groups in this series, an adequate number of patients would be very large even if the permissible error were 10%. Alternation of cases is unnecessary, since uniformity of virulence and of resistance may not be expected. This consideration suggests that hitherto an insufficient number of cases has been made to serve as the basis of a study in which the method of alternation is utilized.

TABLE 1.—LOBAR PNEUMONIA. PATIENTS IN THE HOSPITAL OF THE ROCKEFELLER INSTITUTE, FEBRUARY, 1911, TO JULY, 1932.

	Total patients.	Number recovered.	Number died.	Mortality, %.
Men . . . . .	1063	862	201	18.9
Women . . . . .	393	307	86	21.9
Total . . . . .	1456	1169	287	19.7

*Method.* For the investigation now to be reported an analysis of the records of 1456 patients observed in the Hospital of the Rockefeller Institute has been undertaken (Table 1). The patients were treated during a period of 21 years, from 1911 (February) to 1932 (July). Theoretically the length of time may be regarded a disadvantage; practically this is not necessarily the case for a study of the fatalities throughout this period shows that the deviation from the average death rate, month by month, is  $\pm 4.21\%$  and seems negligible. This result compares not unfavorably with that in the Bellevue-Yorkville district in the period when the investigation at the Bellevue Hospital was taking place. Carrying on a study of an infectious disease over a brief period may, in point of fact, present a disadvantage; the time selected may lie within a time of epidemic manifestation. If a longer view is to be taken, spreading the duration of observation may conceivably be an advantage.

## I.

It was necessary first, as already suggested, to decide which "untoward" phases of lobar pneumonia should be singled out for analysis. Traditionally, being alcoholic, and being engaged in

hard labor, have been regarded as unfavorable factors with which to contend in the process of recovery. To the importance of pneumonia as a common cause of death in old age reference is not infrequently made. But there are other untoward factors beside age, alcoholism, and hard work. These have been analyzed each by itself. Those which, among others no doubt, have an influence on the outcome are apparently:

- A. Type of work (Fig. 1).
- B. Type of pneumococcus (Fig. 2).
- C. Age (Fig. 3).
- D. Alcoholism (Fig. 4).
- E. Bacteriemia (Fig. 5).
- F. Number of lobes involved (Fig. 6).
- G. Cardiovascular affections (Fig. 7).
- H. Complications (Fig. 8).\*

Having done heavy work presents an added risk; so does infection with pneumococcus Types II and III†; age is distinctly a factor and is the more serious the higher the decade, the risk being 3 times greater after than before the age of 40; mild alcoholism is apparently of no consequence; the presence of bacteriemia quadruples the danger and its continued presence raises it about 8 times; involvement of more than two lobes of the lungs raises the risk from 24% (two lobes) to 41% (three lobes) and to 75% and 100% when four and five lobes, respectively, are involved; the complications which were encountered have varying significance, the important ones being empyema when not operated upon, pulmonary abscess, meningitis, pulmonary, renal and cardiac affections. In the sense that heavy work, infection with pneumococcus Types II and III, age over 40, more than moderate use of alcohol, bacteriemia, cardiovascular affections and certain complications have been regarded as factors having an unfavorable influence, so may lighter or less severe phases in each of these categories be grouped and the rates of mortality of patients affected by them be calculated. When this is done (Fig. 9) it appears that the rate is uniformly low—lower distinctly in each class than when the severer phase in that class is experienced.

Certain possible factors seem, on the other hand, to have had no importance in the outcome:

- 1. The number of previous attacks of pneumonia.
- 2. Serum sickness, after specific therapy with serum.

The influence of specific and other forms of therapy requires separate analysis. In this study they have not been taken into consideration. Nor has treatment with antipneumococcus serum

\* These elements will be referred to occasionally by letter.

† Since this analysis deals with cases admitted to hospital before July 1, 1932, further division of these types, subsequently described, could naturally not be regarded.

Type I, given to most patients infected with Type I pneumococcus.\*  
Type II antiserum was given to a few patients only.

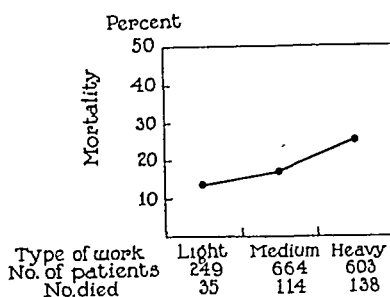


FIG. 1.—Lobar pneumonia. The curve of mortality according to occupation.

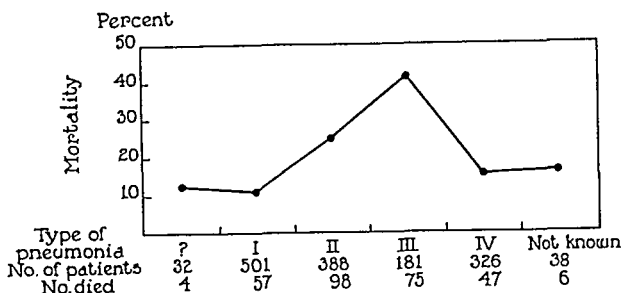


FIG. 2.—Lobar pneumonia. The curve of mortality according to the type of pneumococcus.

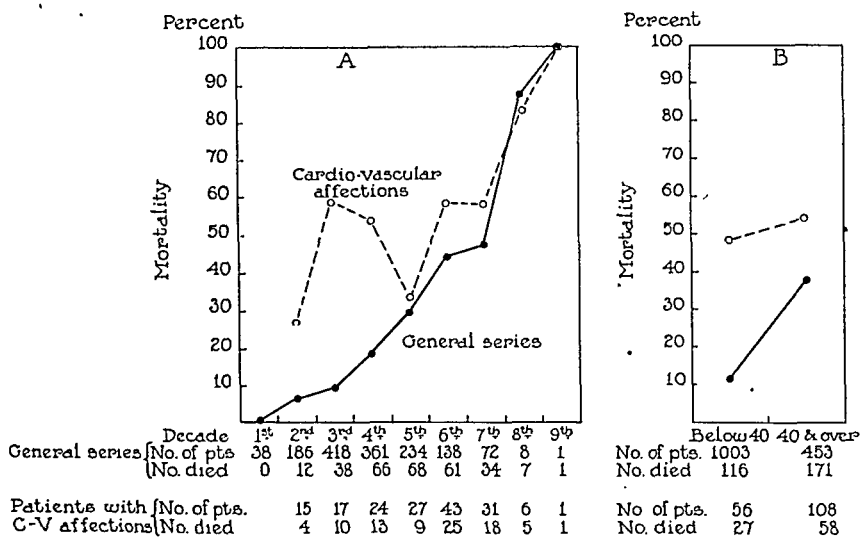


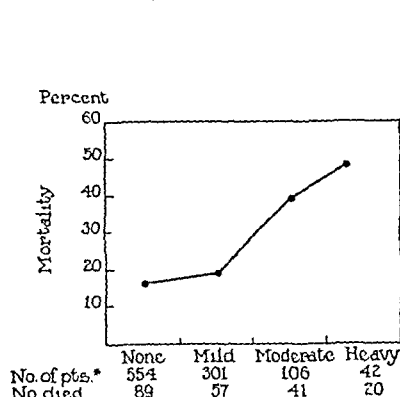
FIG. 3.—Lobar pneumonia. The curve of mortality: A, according to age; B, below and above age of 40.

But important as it is to recognize these individual risks and to assign relative values to them, it is more important still, as has

\* The justification for omitting a further analysis of the influence of therapeutic serum in lobar pneumonia due to pneumococcus Type I, is that cases belonging to this group are regarded in this study as exhibiting a "benign" rather than a "disadvantageous" factor (Fig. 9), except under those circumstances indicated in the footnote to Table 4.

been pointed out, to understand that patients present them not in isolation but in combination. Patients are wholes.

When none of the untoward factors was present death was rare, there being only 2 deaths among 288 patients (0.69%) (Fig. 10).\*



\*No information is given in 453 records

Fig. 4

Fig. 4.—Lobar pneumonia. The curve of mortality according to the use of alcohol.

Fig. 5.—Lobar pneumonia. The curve of mortality according to the presence of bacteriemia.

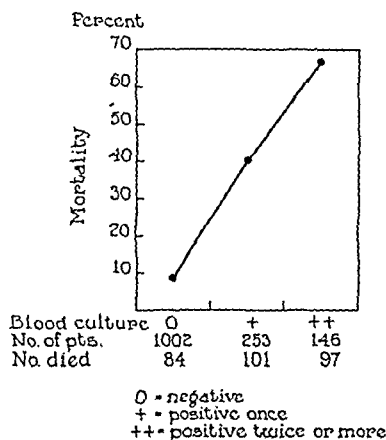


Fig. 5

0 = negative  
+ = positive once  
++ = positive twice or more

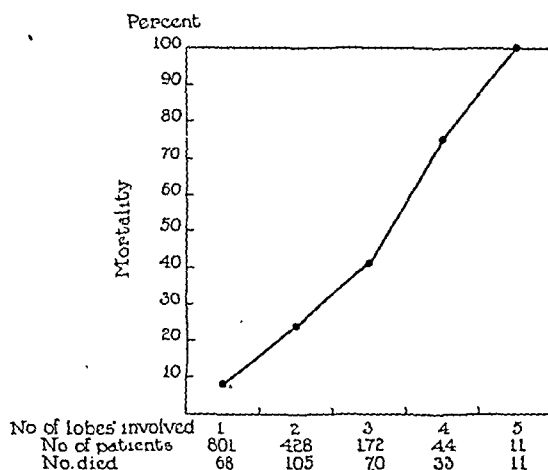


Fig. 6

Fig. 6.—Lobar pneumonia. The curve of mortality according to the number of pulmonary lobes involved.

Fig. 7.—Lobar pneumonia. The curve of mortality according to the presence of cardiovascular affections.

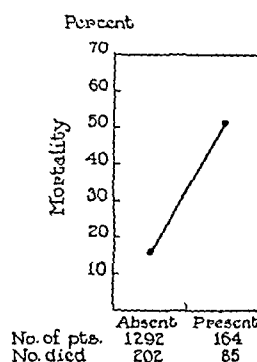


Fig. 7

\* The records of the 2 patients are:

1. A male clerk, aged 17, was admitted on the 11th day of his disease and died 14 hours later. Both lower lobes were involved. The sputum was rusty. The type of organism was not ascertained.

2. A young tailor, aged 21, was admitted on the 4th day of disease and died 25 hours later. The right lower lobe was involved with Type I pneumococcus. Blood culture was sterile. He was given 155 cc. antipneumococcus serum. His electrocardiogram was normal. At autopsy there was consolidation of the right lower lobe; there was absence (congenital?) of the right middle lobe; the heart was negative.

TABLE 2.—LOBAR PNEUMONIA. MORTALITY WHEN ONE† AND TWO UNFAVORABLE FACTORS ARE PRESENT.

	A. Heavy work.			B. Pneumococ. Type II or III.			C. Age 40 and over.			D. Indulgence in alcohol.			E. Bacteriemia Type I or IV.			F. Three or more lobes involved.			G. Cardiovascular affections.			H. Unfavorable complications.		
	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.	Total patients.	Died. No.	Died. %.
A. Heavy work . . . . .	145	1	<b>0.69</b>																					
B. Pneumococcus Type II or III . . . . .	64	4	6.2	124	3	2.4																		
C. Age 40 and over . . . . .	29	0	0.0	59	8	13.6	67	3	<b>4.5</b>															
D. Indulgence in alcohol . . . . .	16	1	6.3	7	0	0.0	10	2	20.0	12	1	<b>8.3</b>												
E. Bacteriemia . . . . .	*34	3	8.8	25	9	36.0	*27	7	25.9	*4	2	50.0	*61	6	<b>9.8</b>									
F. Three or more lobes involved . . . . .	9	1	11.1	19	2	10.5	8	2	25.0	1	0	0.0	*11	4	36.4	17	2	<b>11.8</b>						
G. Cardiovascular affections . . . . .	7	0	0.0	8	2	25.0	11	2	18.2	..	..	..	*1	0	0.0	1	1	100.0	10	1	<b>10.0</b>			
H. Unfavorable complications . . . . .	..	..	..	2	0	0.0	..	..	..	..	..	..	*2	1	50.0	..	..	..	..	..	..	1	1	<b>100.0</b>
Totals 355	159	9	..	120	21	..	56	13	..	5	2	..	14	5	..	1	1	..	..	..	..	..	..	..
Died 51 (14.4%) . . . . .																								

\* This rubric relates to infection with Type I or Group IV (two unfavorable factors). Infection with Pneumococcus Type II or Type III results in three unfavorable factors.

† Bold face type indicates the rate of mortality when single untoward factors were present.



When *one* untoward factor only was present (Table 2; Fig. 11) the outlook was favorable or at least not unfavorable, though even under these circumstances the nature of the factor was not without

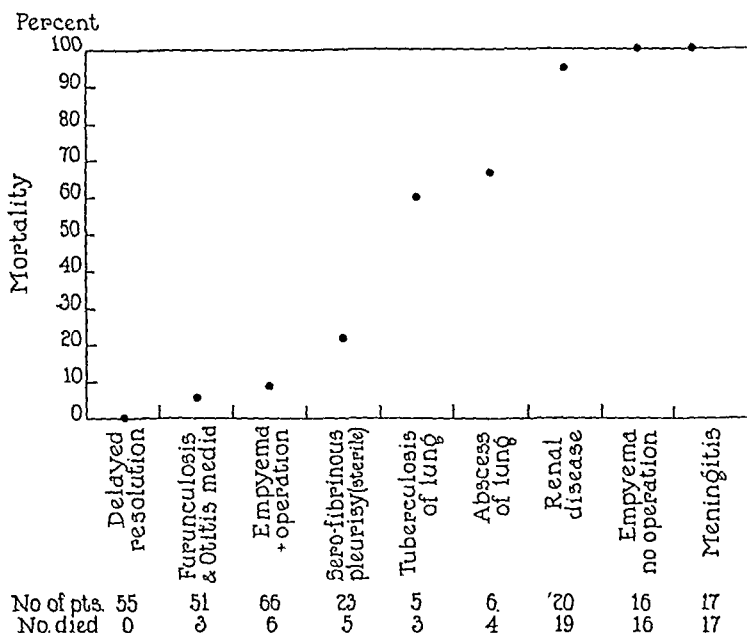


FIG. 8.—Lobar pneumonia. The curve of mortality according to the complications present, exclusive of cardiovascular affections.

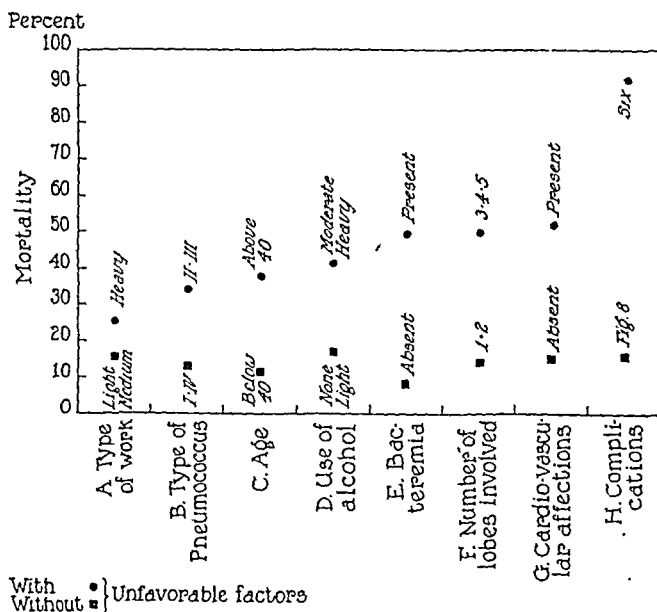


FIG. 9.—Lobar pneumonia. The curve of mortality with and without the presence of "unfavorable" factors.

importance. The number of patients who were observed in the Classes *F*, *G*, *H* was, however, too small to permit reliable inference. When *more than one* of the untoward factors was present the rate

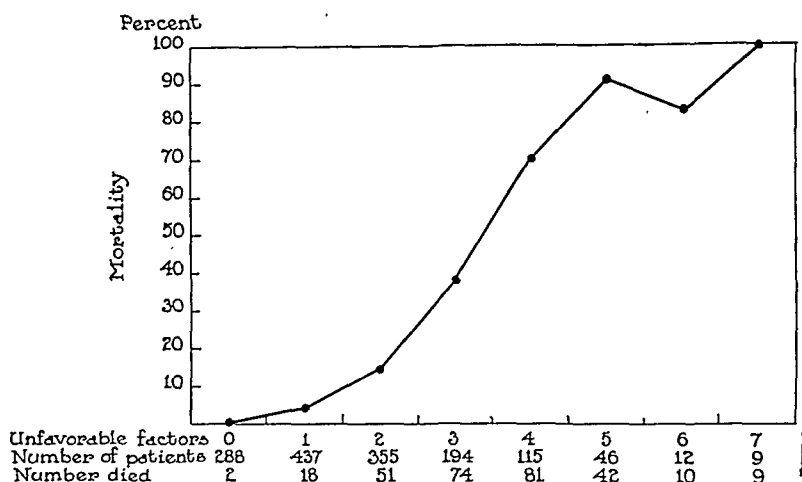


FIG. 10.—Lobar pneumonia. The curve of mortality according to the number of "unfavorable" factors.

of mortality rose (Fig. 10), depending on the number of them with which patients were obliged to deal. With *two* the rate was 14.4% (Table 2); with *three* it began to rise rapidly.

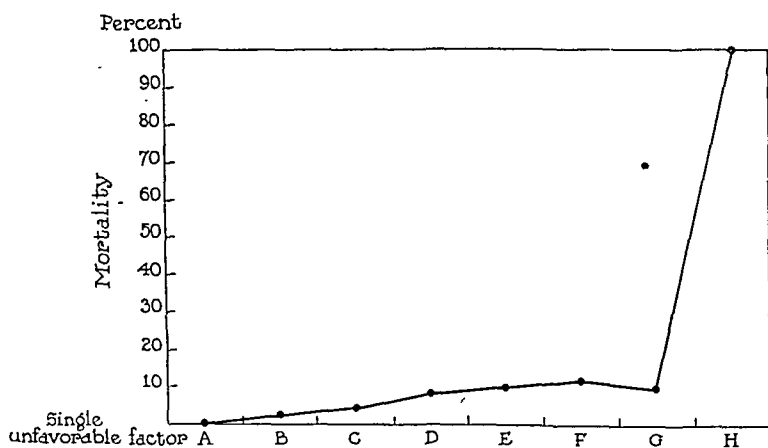
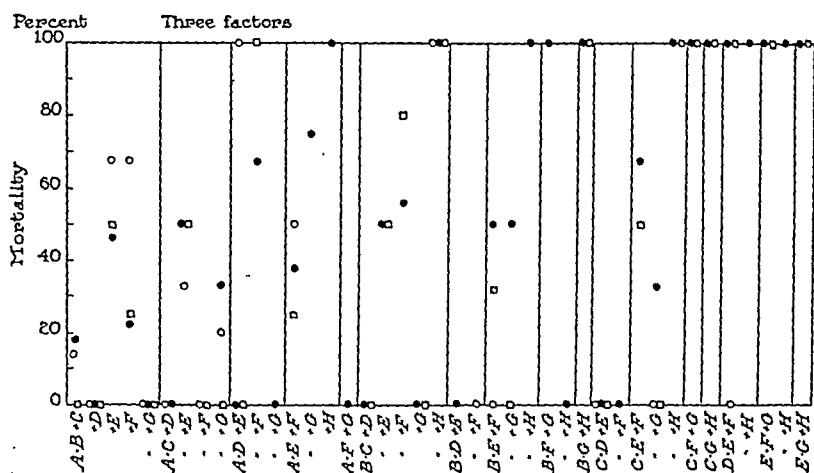
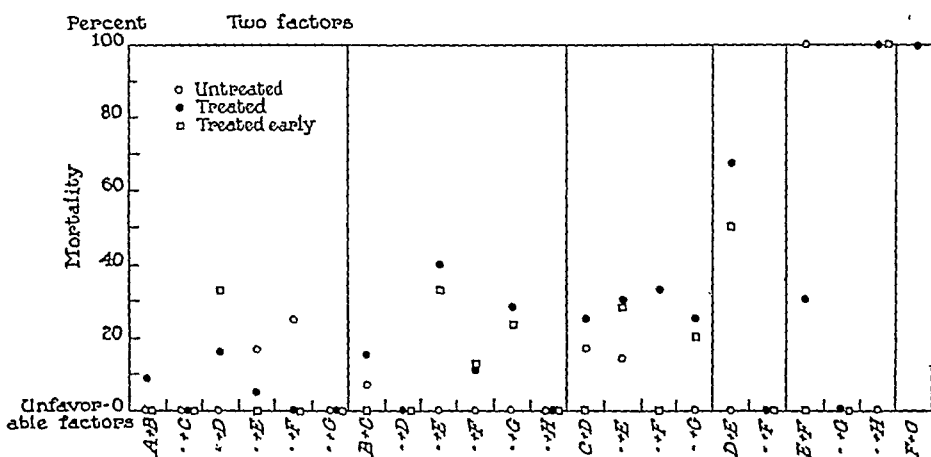
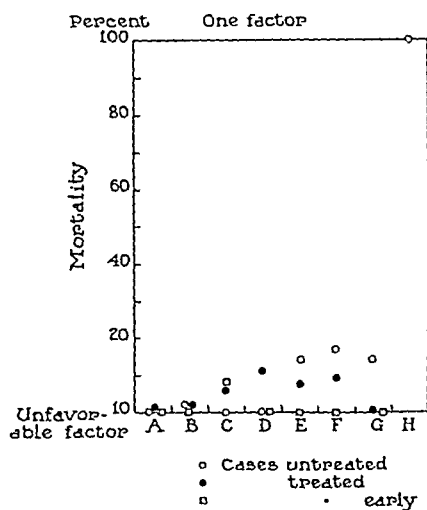


FIG. 11.—Lobar pneumonia. The curve of mortality according to the presence of single "unfavorable" factors. Category *H* includes only 1 case.

An attempt has been made to discover whether there is an arrangement or combination of factors which would prove to be more or less likely to influence the course of pneumonia than another combination. There was studied first what the result would be if any two factors were placed in combination, then any three, and so



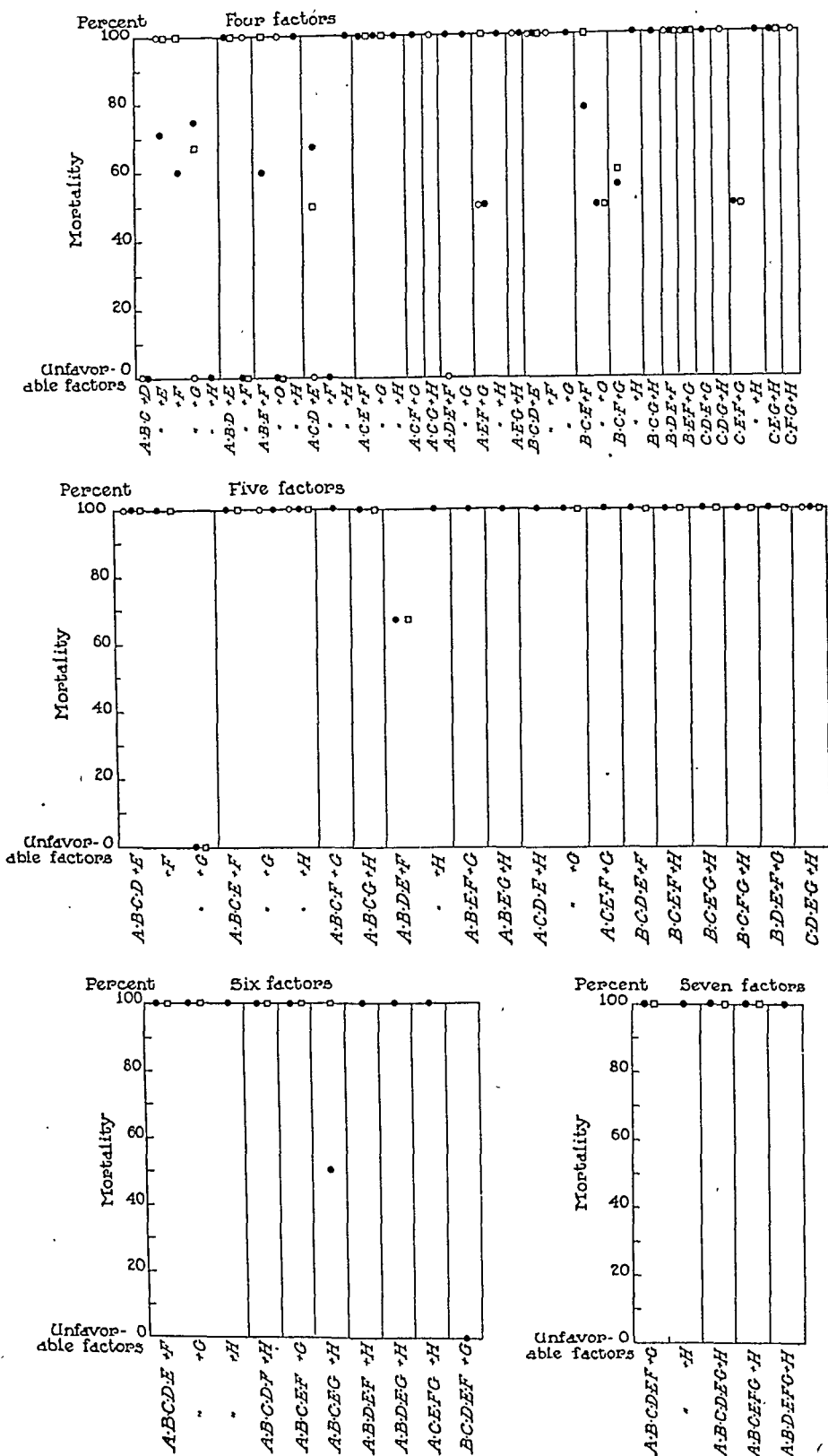


FIG. 12.—Lobar pneumonia. Mortality is shown according to the distribution of eight unfavorable factors in every actual combination.

TABLE 3.—LOBAR PNEUMONIA. MORTALITY OF PATIENTS TREATED WITH AND WITHOUT

ALL PATIENTS.			DIGITALIS. In First 72 Hours of Disease.													
No.	Died.	Mor- tality, %	Group.	Dose, gm.	No unfavorable factor.			One unfavorable factor.			Two unfavorable factors.			Three unfavorable factors.		
					No. pts.	No. died.	Mor- tality, %.	No. pts.	No. died.	Mor- tality, %.	No. pts.	No. died.	Mor- tality, %.	No. pts.	No. died.	Mor- tality, %.
			I	0.1-0.6	30	0	0	31	1	3.23	18	1	5.55	6	1	16.7
			II	0.7-0.8	13	0	0	14	0	0.0	13	1	7.7	7	2	28.6
			III	0.9-1.5	28	0	0	70	1	1.43	70	7	10.0	35	14	40.0
			IV	1.6+	3	0	0	20	1	5.0	21	3	14.3	14	6	42.9
			Total		74	0	0	135	3	2.22	122	12	9.84	62	23	36.8
698	117	16.7														
After 72 Hours.																
			V	0.1-0.6	28	1	3.6	43	1	2.3	26	8	30.8	22	16	72.7
			VI	0.7-0.8	5	0	0	27	1	3.7	17	5	29.4	5	3	60.0
			VII	0.9-1.5	30	0	0	70	4	5.7	77	13	16.9	40	13	32.5
			VIII	1.6+	6	0	0	16	2	12.5	27	6	22.2	22	8	36.4
			Total		69	1	1.45	156	8	5.1	147	32	21.8	89	40	44.9
758	170	22.4														
Total	1,456	287	19.7													
Mortality of Patients Untreated and Treated With Digitalis.																
Digitalis					143	1	0.70	201	11	3.78	269	44	16.3	151	63	41.7
No digitalis					145	1	0.69	146	7	4.79	86	7	8.1	43	11	25.6
Difference					+0.01			-1.01			+8.2			+16.1		
Mortality of Patients Untreated and Treated With Digitalis Groups II and III.																
Digitalis Groups II and III					41	0	0	84	1	1.19	83	8	9.6	42	16	38.1
No digitalis					145	1	0.69	146	7	4.79	86	7	8.1	43	11	25.6
Difference					-0.69			-3.60			+1.5			+12.5		

\* See Fig. 15.

on to any eight factors (Fig. 12). But all these efforts have been without great significance. When *E*, *F*, *G*, *H* are elements in the combination the mortality is higher, but the numbers in these groups, occurring in isolated fashion, or indeed in any fashion at all, are too small for reliable calculation. Except for this reservation, the inference seems to be justified that the presence of what may be "extras" in the disease lobar pneumonia has a bearing on the outcome. The number of them with which a patient must grapple has obviously an important influence. It is desirable to know what added burden each one contributes, but to be certain what this is, the numbers available in this and in other studies are too small to ascertain. The untoward factors of which account has been taken are obviously heterogeneous. Some have and some

## DIGITALIS. GROUPED ACCORDING TO THE NUMBER OF UNFAVORABLE FACTORS.\*

DIGITALIS. In First 72 Hours of Disease.															WITHOUT DIGITALIS.					
Four unfavorable factors.			Five unfavorable factors.			Six unfavorable factors.			Seven unfavor- able factors.			No.	Died.	Mor- tality. %	No.	Died.	Mor- tality. %			
No. pts.	No. died.	Mor- tality, %.	No. pts.	No. died.	Mor- tality, %.	No. pts.	No. died.	Mor- tality, %.	No. pts.	No. died.	Mor- tality, %.									
4	3	75.0	6	6	100	1	1	100	1	1	100	97	14	14.4						
0	..	..	1	1	100	0	..	..	0	..	..	48	4	8.3						
24	20	83.3	7	7	100	3	3	100	1	1	100	238	53	22.3						
10	8	80.0	6	4	66.7	1	1	100	1	1	100	76	24	31.6						
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
38	31	79.5	20	18	90.0	5	5	100	3	3	100	459	95	20.7	239	22	9.2			
After 72 Hours.																				
11	7	63.6	1	1	100	1	1	100	3	3	100	135	38	28.2						
7	5	71.4	1	1	100	1	1	100	0	..	..	63	16	25.4						
24	18	75.0	9	8	88.9	4	2	50	2	2	100	256	60	23.4						
15	6	40.0	7	7	100	1	1	100	1	1	100	95	31	32.7						
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						
57	36	63.1	18	17	94.4	7	5	71.4	6	6	100	549	145	26.5	209	25	12.0			
															1,008	240		448	47	
Mortality of Patients Untreated and Treated With Digitalis.																				
95	67	70.5	38	35	92.1	12	10	83.3	9	9	100									
20	14	70.0	8	7	87.5	0	..	..	0	..	..									
+0.5			+4.6																	
Mortality of Patients Untreated and Treated With Digitalis Groups II and III.																				
24	20	83.3	8	8	100.0															
20	14	70.0	8	7	87.5															
+13.3			+12.5																	

have no necessary connection with lobar pneumonia. They have only this importance, that they are presented by patients during the course of this disease.

## II.

Having separated the cases into groups according to their severity it became possible to study the effect of the action of digitalis in each group. Since the time in the course of the disease at which digitalis is given might exert an influence, this point has been taken into account. In those who recovered the duration ends with crisis or lysis in 7.9 days; in those who died, in 7.88 days. "Early" has been regarded, therefore, as the first 72 hours (Fig. 13); "late," as the remainder of the duration. Since digitalis was given, so far as concerns the entire experience, in an irregular manner, it

has been necessary to take dosage also into consideration. There are patients who took none; others who took small (Groups I and V), moderate (Groups II and VI), sufficient (Groups III and VII) and large amounts (Groups IV and VIII). Each group was divided

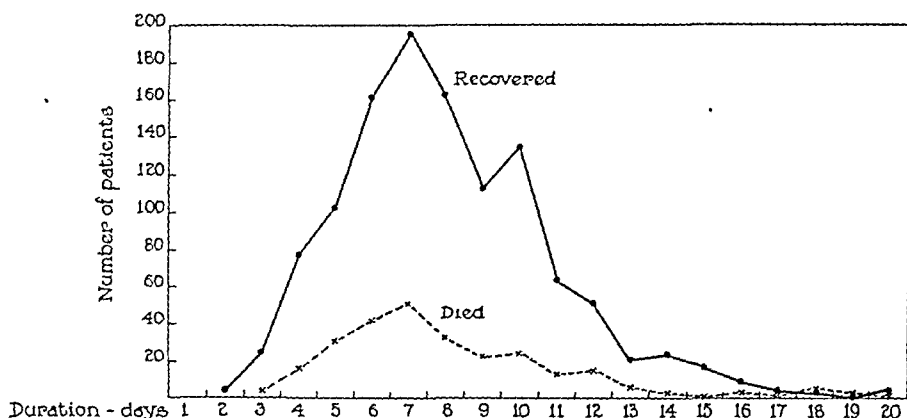


FIG. 13.—Lobar pneumonia. This curve shows the number of cases of recovery and of death according to the number of days of illness. The average duration of illness of the *recovered* cases, excluding 7 cases lasting longer than 20 days, was 7.9 days; of *fatal* cases, excluding 11 cases lasting longer than 20 days, was 7.88 days; of all cases was 7.89 days.

according to whether digitalis was taken early or late. Except for the patients to whom strophanthin was given, digipuratum or digitan (Knoll, Merck) has been used almost uniformly. Since 0.9 to 1 gm. has affected the ventricular rate of patients the subject

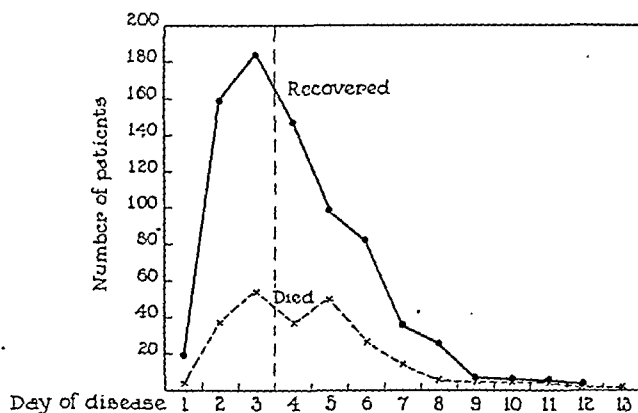


FIG. 14.—Lobar pneumonia. This curve shows the number of cases of recovery and of death according to the day on which digitalis was first administered. The first 3 days are regarded as being "early" in the course of the disease.

of auricular fibrillation ill of pneumonia, 0.9 to 1.5 gm. has been taken to be a "sufficient" dose. The cases have been divided, therefore, in groups, depending on the time of administration

(Fig. 14) and on size of the dose of digitalis administered (Table 3). These considerations have been utilized in analyzing the effect of giving digitalis to patients, depending on the "severity of disease," severity being expressed in terms of the number of untoward phenomena which developed in its course (Table 3). The tables show that there appears to be little difference whether digitalis was taken or not, except when two, three and five untoward factors were present (Table 3). If a sufficient dose (0.9 to 1.5 gm.) was given "early" (Fig. 15) the mortality was less than when no digitalis was taken in those without or with one untoward factor; it was greater otherwise, but the difference is not important. If the time when digitalis was given is regarded, the mortality was less in those with-

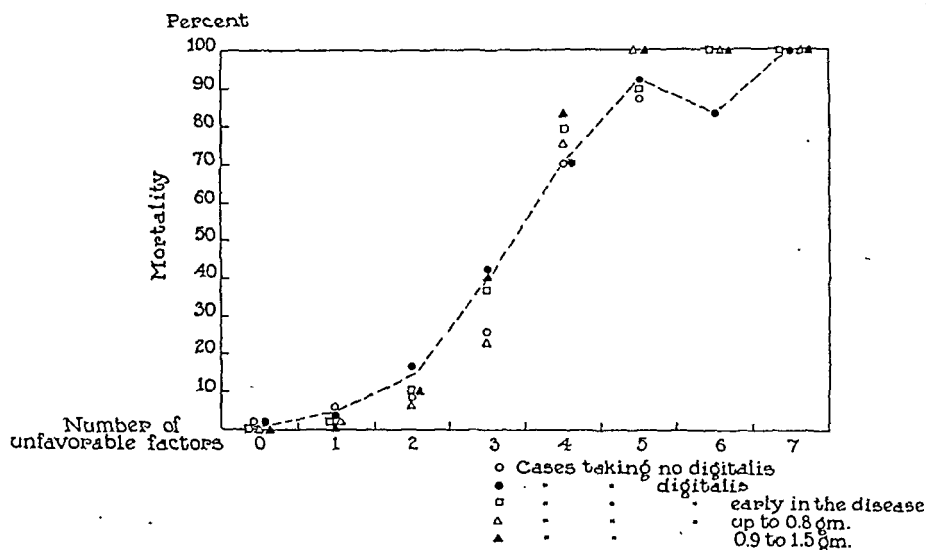


FIG. 15.—Lobar pneumonia. The mortality is exhibited of patients when untreated and treated with digitalis, when digitalis was given early, and when up to 0.8 gm., and when 0.9 to 1.5 gm. were given, early in the disease. The broken line describes the curve of mortality of the general series.

out or with one untoward factor; otherwise it was greater, but again the difference is slight. If small doses of digitalis (up to 0.8 gm.) were given the death rate was smaller when there were none, one, two or three of these factors. But the differences again are small.

The attempt finally has been made to discover whether, among the untoward elements, certain ones, when they were present alone, played a rôle more or less unfavorable than others when digitalis was given. The aged and the alcoholic were not aided; otherwise it did no harm (Table 4). Where the differences appear large in either direction the numbers of cases are too small to yield significant results. Whether digitalis was given or was not, whether the size of the dose was small or, in our judgment, adequate, whether it was given early or late—all of these considerations appear to be



of no deciding consequence. The form of the curve of mortality (Fig. 15) depends, it seems, entirely on the degree of severity of the affection; when it is slight, death is rare; the more severe, the greater the number of untoward factors against which the struggle must be made, the smaller become the chances of recovery. The form of the curve appears to indicate what the important factor is in deciding the outcome; it is the disease—virulence of the infection and resistance of the host, both together, rather than the action of digitalis.

TABLE 4.—LOBAR PNEUMONIA. MORTALITY OF PATIENTS TREATED AND UNTREATED WITH DIGITALIS EXHIBITING A SINGLE UNFAVORABLE FACTOR.

	No digitalis.			Digitalis.			Difference in mortality, %.
	No. of patients.	Died.	Mortality, %.	No. of patients.	Died.	Mortality, %.	
A. Heavy work . . . . .	48	0	0.0	97	1	1.03	1.03
B. Type II or III* pneumococcus . . . . .	43	1	2.33	81	2	2.47	0.14
C. Over 40 years of age . . . . .	17	0	0.0	50	3	6.00	6.00
D. Moderate or heavy use of alcohol . . . . .	3	0	0.0	9	1	11.1	11.1
E. Bacteriemia* Type I or Group IV . . . . .	21	3	14.3	40	3	7.5	-6.8
F. Three or more* lobes involved . . . . .	6	1	16.7	11	1	9.1	-7.6
G. Cardiovascular affection . . . . .	7	1	14.3	3	0	0.0	-14.3
H. Unfavorable complications . . . . .	1	1	100.0				
Total . . . . .	146	7	4.79	291	11	3.78	-1.01

\* The presence of infection with *Pneumococcus* Type I or Group IV is not counted as an untoward factor except when it invades the blood stream or when 3 or more lobes are involved. *Pneumococcus* Type II and Type III when they are accountable for the existence of lobar pneumonia and are present also in the blood or when 3 or more lobes are involved are counted as two factors; cases so affected are not included in this table.

### III.

If, in this stage of the analysis an interpretation were adopted which would be regarded as reasonable, it would be that giving digitalis to patients with lobar pneumonia does not influence the rate of mortality; this method of analytical treatment points neither to an unfavorable nor to a beneficial action. But numerous physicians<sup>6-15</sup> maintain the belief that the course of disease in those to whom digitalis has been given is influenced nevertheless. The difficulty consists, has indeed consisted, in putting this belief to test. If the method of study so far adopted leads to an *impasse*, another approach to solving this problem may be attempted.

The beneficial action of digitalis is most convincing in patients with certain affections of the heart, of course not subjects of lobar pneumonia. Proof that digitalis acts upon the heart is no longer

necessary. That it acts also upon the febrile heart in pneumonia<sup>1</sup> seems now generally to be accepted. Aside from having an influence on the size of the heart in pneumonia, digitalis exercises its well-known action on conduction by reducing the rate of the ventricles in auricular fibrillation. The view has been expressed that it is precisely in cases of auricular fibrillation<sup>2, 10-13</sup> and auricular flutter in which, because with the onset of these irregularities serious symptoms develop, perhaps resembling the state sometimes called collapse, giving digitalis actually has a beneficial action. As a result of early experiences in the Hospital of the Rockefeller Institute the point was made that, since many cases of auricular fibrillation and flutter occurred (11 in 123, 9.7%) in which it did good,

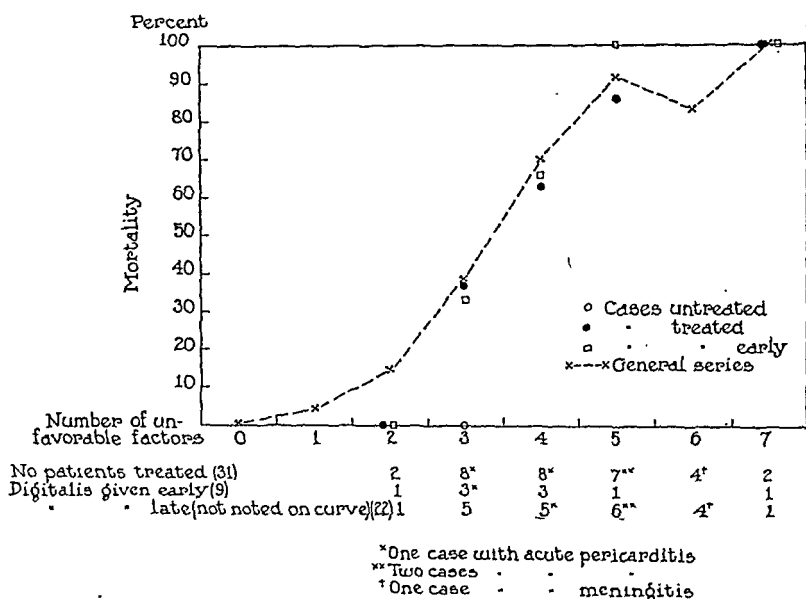


Fig. 16.—Lobar pneumonia and auricular fibrillation. The mortality of patients untreated and treated with digitalis according to the number of "unfavorable" factors, of which auricular fibrillation or flutter was one, which were present, exhibited in relation to the curve of mortality of the general series.

digitalis might be given as routine treatment with the view, in anticipation of its occurrence, of preventing harm due to this arrhythmia.<sup>17</sup> The point had not yet been appreciated that younger individuals rarely exhibited this irregularity; and that it occurred for the most part only beginning with the fifth decade. Since an effect occurred on heart muscle, as seen in changes in the *T* wave,<sup>1</sup> on the size of the heart<sup>16</sup> and on contraction with moderate doses, the statement<sup>1</sup> was made that action by digitalis could be counted on—whether for good was another matter. At all events, the effect on conduction in auricular fibrillation might prove to be life saving.

In the light of these reflections, the course of events in all the cases of auricular fibrillation and auricular flutter has been reviewed

(31 patients, of whom 18 [58%] died).<sup>\*</sup> The cases have been analyzed, though the number is small, from the point of view of the general mortality, of the age of the patients, of the other untoward factors which they presented. It is apparent that, if the cases are grouped according to the number of the "untoward" factors against which they were required to contend, the outcome in those who suffered from two (of which auricular fibrillation was one) was strikingly better than that in the general series (Fig. 16). When there were three factors (of which auricular fibrillation was one) the death rate was actually lower than the rate in the case of those who took digitalis (Fig. 16). The 3 patients who died were seriously ill (Fig. 16). When there were more untoward factors there was no important difference from the general curve of mortality. The influence of age on the development of auricular fibrillation is not certain; the number of cases is too small. One only occurred before the age of 30; the incidence then rose to the age of 60 and in the seventh and eighth decades fell (Fig. 17).<sup>†</sup>

Whatever may be learned from greater experience concerning the influence of fibrillating auricles on the outcome of lobar pneumonia, this at all events is apparent from the few observations which it has been possible to make; the chances in those in whom it is present are not worse than in other patients (Fig. 16). Giving digitalis has been useful when no more than two untoward elements (besides auricular fibrillation itself) were present; the rate of mortality was favorably influenced. When there were more untoward

<sup>\*</sup> A table containing full data of these cases has been made and will gladly be placed at the disposal of those who are interested in studying it.

<sup>†</sup> Several notes concerning the cases in which auricular fibrillation occurred deserve record:

Of 31 patients taking digitalis:

1. (a) Auricular fibrillation persisted until death . . . . .	8 (26%)	8
Auricular fibrillation persisted in recovery . . . . .	1 (3%)	
(b) Ventricular rate slowed . . . . .	23 (74%)	
(c) Normal rhythm returned . . . . .	22 (71%)	
Of whom 12 (39%) recovered		
Of whom 10 (32%) died . . . . .		10
		<hr/> 18

13 patients recovered:

2. (a) Auricular fibrillation developed before taking digitalis . . . . .	8	
(b) Auricular fibrillation developed after taking digitalis, 1 gm. . . . .	2	
(c) Auricular fibrillation developed after taking digitalis, less than 0.9 gm. . . . .	3	
		<hr/> 13

18 patients died:

3. (a) Auricular fibrillation developed before taking digitalis . . . . .	6	
(b) Auricular fibrillation developed after taking digitalis, 0.5 gm. . . . .	1	
(c) Auricular fibrillation developed after taking digitalis, 1 to 2.2 gm. in 2 to 5 days . . . . .	11	
		<hr/> 18

Number of cases before taking digitalis (a) 14 (2a + 3a) of whom 6 died (42.9%)

Number of cases having taken a sufficiency of digitalis (b) 13 (2b + 3c) of whom 11 died (85.0%)

elements, the chances were not worse than they would otherwise have been.

Although there is no reason to believe that the study of patients suffering from other forms of cardiac affection can throw light on

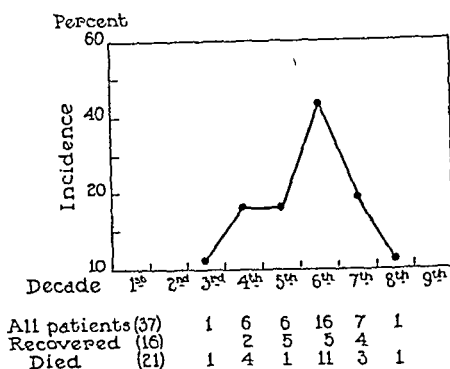


FIG. 17.—Lobar pneumonia and auricular fibrillation. This curve exhibits the patients arranged according to age.

the value of giving digitalis, the experience gained from 164 cases in which some form of cardiac affection was detected has been analyzed. Mortality according to age lay higher in the earlier decades in relation to the general series than in the later ones

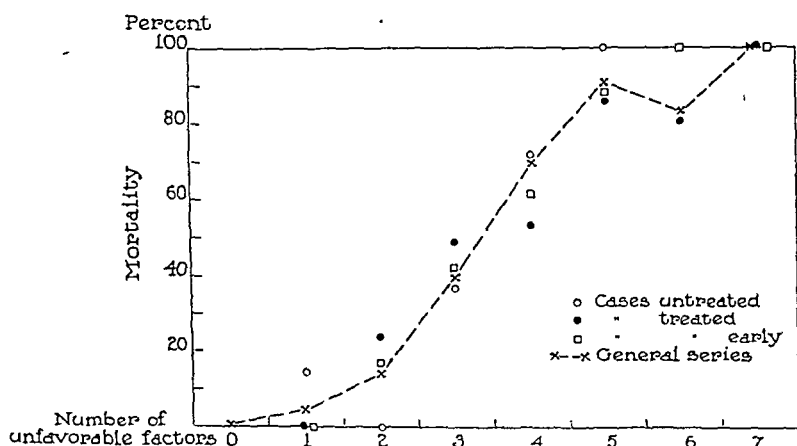


FIG. 18.—Lobar pneumonia and cardiovascular affections. The mortality of patients untreated and treated with digitalis, according to the number of "unfavorable" factors, of which cardiovascular affections was one, which were present, exhibited in relation to the curve of mortality of the general series. Compare Table 7.

(Fig. 3). A variety of irregularities and of organic diseases (of the valves, arteriosclerosis and hypertension, acute pericarditis) were encountered (Tables 5 and 6). In these cases the influence of the action of digitalis on the curve of mortality exhibits no important

difference from that which occurred in the general series (Table 7; Fig 18).

TABLE 5.—LOBAR PNEUMONIA AND CARDIOVASCULAR AFFECTIONS. MORTALITY ACCORDING TO TYPE OF AFFECTION.

A.*	Type of affection.	Number.	Died.	Mortality, %.
Arrhythmia:				
	Premature contractions . . . . .	49	20	41.7
	Auricular fibrillation . . . . .	37	21	56.8
	Valvular disease . . . . .	27	14	51.9
	Coronary sclerosis	28	16	57.5
	Hypertension			
	Arteriosclerosis			
	Acute pericarditis . . . . .	29	29	100.0
B.†				
	Heart block . . . . .	23	3	13.1

\* See Figs. 3 and 7.

† See Table 6.

TABLE 6.—LOBAR PNEUMONIA AND HEART BLOCK.

Case No.	Age, years.	Type of heart block.	Auriculo-ventricular conduction time, sec.	Occurrence of heart block; relation to fever.	Amount given before onset of heart block.	Duration of heart block.	Result.
1072	40	2:1 Auricular fibrillation	Increased Varying	During	Strophanthin 3 x 1 mg. i.v.	Transient	Recovered
4046	69	Long A-V interval and 2:1 Auricular fibrillation	0.12-0.38	During	Strophanthin 2 x 1 mg. i.v.	Transient	Died
3488.	24	Long A-V interval and 2:1	0.18-0.34	During	Digitalis 2.6 gm.	Transient	Recovered
5698	34	Long A-V interval and 2:1	0.22-0.34	During	Digitalis 1.1 gm.	Transient	Recovered
6164	31	Long A-V interval and 3:2	Increased Varying	During	Digitalis 2.0 gm.	Transient	Recovered
5206	28	3:2	0.20	During	Digitalis 0.8 gm.	Transient	Recovered
2247	43	Long A-V interval and 2:1	0.22-0.34	During	Digitalis 2.9 gm.	Transient	Died
7904	65	Left bundle branch block (0.14 seconds)	0.16	During	Digitalis 0.9 gm.	Permanent	Died
3164	22	Long A-V interval and 2:1	Increased Varying	During and after	Digitalis 1.5 gm.	Transient	Recovered
6922	15	2:1	Increased Varying	After	Digitalis 1.1 gm.	Transient	Recovered
2102	18	Occasional blocked auricular beats	0.22-0.28	After	Digitalis 1.9 gm.	Transient	Recovered
3658	19	Long A-V interval and 2:1	0.12-0.28	After	Digitalis 2.0 gm.	Transient	Recovered
2351	23	Long A-V interval and 2:1	0.18-0.32	After	Digitalis 2.1 gm.	Transient	Recovered
2222	26	Long A-V interval and 2:1	0.15-0.34	After	Digitalis 1.5 gm.	Transient	Recovered
5427	32	2:1 and 3:1	Increased Varying	After	Digitalis 1.1 gm.	Transient	Recovered
3169	45	2:1	Increased Varying	After	Digitalis 3.1 gm.	Transient	Recovered
3914	56	2:1	Increased Varying	After	Digitalis 2.0 gm.	Transient	Recovered
6664	34	Sino-auricular block	Increased Varying	After	Digitalis 1.0 gm.	Transient	Recovered
5077	42	Occasional blocked auricular beats	Increased Varying	After	Digitalis 0.9 gm.	Transient	Recovered
3319	18	3:2	Increased Varying	After	Digitalis 1.6 gm.	Transient	Recovered
7308	56	Slight right intraventricular block (0.12 second)	0.14-0.16	After	Digitalis 1.0 gm.	Transient	Recovered
6574	42	Slight right intraventricular block (0.12 second)	0.16	During	Digitalis 1.0 gm.	? Permanent	Recovered
4131	34	Right intraventricular block (0.16 second)	0.13	During and after	...	Permanent	Recovered

TABLE 7.—LOBAR PNEUMONIA AND CARDIOVASCULAR AFFECTIONS. MORTALITY OF PATIENTS UNTREATED AND TREATED WITH DIGITALIS ACCORDING TO NUMBER OF UNFAVORABLE FACTORS OF WHICH A CARDIOVASCULAR AFFECTION WAS ONE.\*

No. of unfavorable factors.	No digitalis.			Digitalis.								
	No. of patients.	Mortality.		All patients.			Digitalis given early.			Digitalis given late.		
				No. of patients.	Mortality.		No. of patients.	Mortality.		No. of patients.	Mortality.	
		No.	%.		No.	%.		No.	%.		No.	%.
1	7	1	14.3	3	0	0.0	1	0	0.0	2	0	0.0
2	6	0	0.0	22	5	23.6	12	2	16.7	10	3	30.0
3	11	4	36.4	33	16	48.5	12	5	41.7	21	11	52.4
4	7	5	71.4	34	18	52.9	18	11	61.0	16	7	43.8
5	2	2	100.0	21	18	85.7	8	7	87.5	13	11	84.6
6	..	..	....	10	8	80.0	3	3	100.0	7	5	71.4
7	..	..	....	8	8	100.0	3	3	100.0	5	5	100.0
Total	33	12	36.4	131	73	55.7	57	31	54.4	74	42	56.8

\* See Table 5 A.

**Discussion.** Mention recurs unfortunately with too great frequency of the value of digitalis in the cure of lobar pneumonia. The thought that digitalis can have a bearing on the outcome of the disease itself should disappear. When this idea was originally suggested,<sup>18</sup> relatively little was known either concerning the nature of pneumonia or the action of this drug. It was the fall in temperature which attended the use of large doses that suggested to Traube and others its availability as an antipyretic. No one believes now that digitalis has this property. Another belief concerning its action is bound up with the word beneficial. Beneficial can be used in two senses: (1) Connected with an effect on the disease itself and (2) with the effect on some occurrence, precipitated during its course.

(1) To be beneficial as concerns the disease itself requires proof that there is a relation between the action of digitalis and the pulmonary process. Since there is no evidence for this supposition, this notion also can be dismissed. But (2) that taking digitalis has an effect on a physiologic process (auricular fibrillation) apart from but precipitated in the course of the disease is, however, fairly established.<sup>1,2,3</sup> Conclusions formerly published<sup>1</sup> state that: "(1) Digitalis acts during the febrile period in pneumonia. (2) It produces a beneficial, possibly a life-saving effect in cases of auricular irregularity (fibrillation and flutter). (3) Whatever beneficial action it has on the function of the normally beating non-febrile heart may be expected from its use in the febrile heart of pneumonia." These conclusions point obviously to the action of digitalis on the

heart and not to an action on the immunologic processes of the disease, lobar pneumonia. For these reasons it seems gratuitous to speak of a beneficial effect of the action of digitalis on the rate of mortality. Unless current conceptions dealing with the nature of pneumonia were incorrect, this notion should no longer be suggested. It is only when some untoward accident, like fibrillation of the auricles, occurs that giving digitalis may be regarded as an aid; if people were otherwise to die of this accident, digitalis may be regarded as life saving—but only in this sense and only in this connection. When it was first discovered that transient auricular fibrillation occurred in lobar pneumonia and that it seemed furthermore to occur frequently (9.7% of cases), “as a result of these experiences, the hospital (of the Rockefeller Institute) *for the time being*\* adopted the following rules in the treatment of pneumonia. . . .”<sup>19</sup> With more experience and for reasons already detailed, practice in this regard has changed.

If the use of an agent is found to be beneficial in one respect, as in the management of transient auricular fibrillation, care must be exercised nevertheless to see to it that it is not harmful in another, as in the outcome of lobar pneumonia itself. The evidence, not yet conclusive, indicates that the action of digitalis is without influence on the rate of mortality under a variety of circumstances.

This inference differs from that of Niles and Wyckoff and Wyckoff, DuBois and Woodruff. It is perhaps striking that the difference between their treated and untreated cases is as little as 7.7% (Table 5).<sup>2</sup> This is within the error of most physical, to say nothing of biologic, measurements and speaks for the correctness of the inference in the present study. Why the results of these two studies varies is not certain. The nature of the cases may not have been fundamentally different. Perhaps the difference in technique of the analyses employed in the two hospitals is responsible for the difficulty. And yet when the crude figures alone are regarded, the rate of mortality in both favors the untreated cases. It did in fact occur, as in the experience of other observers, that the patients more severely ill in our hospital took digitalis rather than the others. A conclusion should not depend, however, on so simple a comparison. In the attempt to make comparison valid, reliance has been placed on treating a large number of cases, though perhaps not large enough; since sufficiently large numbers are scarcely available, it has been necessary to resort to some sort of weighing of the evidence.

Essentially it is weighing which has been attempted in this study. Other methods have been employed. Bullowa<sup>5</sup> used the method of rating the severity of each of five main factors, the value given to each factor being, of course, arbitrary. But the reason for doing so is clear: The method of alternation to secure

\* Italics not in original.

controls cannot, in a relatively small group of cases, be undertaken otherwise with justice. The factors which Bullowa rated depend, with the exception of age, pregnancy, and obesity, on phases of the disease. With a different choice of the exceptions, the method this study has pursued is similar. It is possible that, again with a few exceptions, such as *E*, *F*, *G*, *H*, the factors chosen for analysis are of small importance as long as certain ones like bacteriemia are included. The total load patients must bear decides the outcome. Adding other factors like pregnancy, obesity, psychologic disturbances, gastro-intestinal distress, cyanosis, naturally increases the number of variables to 13 and necessitates the accumulation of *still* greater numbers of cases, if justifiable inferences as between the effect on treated and untreated cases are to be drawn.

The matter of weighting becomes the more important when the difficulties are reviewed which unavoidably enter a research so complicated as this. Wyckoff, DuBois and Woodruff, and Niles and Woodruff encountered difficulty with their digitalis Specimen B, which they gave to 142 (42%) of their patients. Now the assay of B was twice that of the other specimens used and the rate of mortality was 10% higher. But when Specimen B made patients ill, the rate of mortality was only 24.6% as against 64.2% when it was not toxic, and as against a rate of 33.7% for the untreated cases. In short, the stronger, toxic, digitalis reduced the rate by 9.1% below that of the untreated cases. In another connection it appears that, when bacteriemia was an unfavorable factor, those who were treated with digitalis were better off by 0.4% than the untreated cases; but freedom from bacteriemia, in those likewise treated with digitalis, reduced their chances of recovery by 14.3% as against those untreated. These are perhaps vagaries; but they are not of a nature to satisfy one of the competence of a method to yield insight into so complicated a situation.

Objections have been made to the use of digitalis in lobar pneumonia<sup>20</sup> on the ground: (1) That auricular fibrillation is rarely found except in dying hearts; and (2) that it has a tendency to excite the onset of auricular fibrillation. If the occurrence of auricular fibrillation is regarded from the viewpoint of the total experience, its incidence was small, 37 in 1456 (2.5%). But after the age of 40 there were actually 6.6%, and under 40, only 0.7%. So far as the tendency to excite the onset of auricular fibrillation is concerned, the evidence to which Wolferth<sup>20</sup> referred is meager. Robinson,<sup>21</sup> in describing his patient, says: "The administration of digitalis may have been a factor in causing the disappearance of auricular fibrillation on two occasions." But neither his case nor others reported in the literature<sup>\*,23,24</sup> occurred in lobar pneumonia. In this series 14 cases occurred before taking digitalis (Foot-

\* Resnik deals critically with the cases collected by Robinson.<sup>22</sup>



note, p. 474, 2a + 3a). A relation may exist, but the evidence so far is scarcely conclusive. It is noteworthy that in 1008 patients, auricular fibrillation was detected no oftener than 35 times (3.5%) among those who took digitalis (including those who took strophanthin). It is worth noticing also that of 31 patients who took digitalis (not strophanthin), the normal rhythm returned in 22, and that 10 of these died. Of the 18 who died, auricular fibrillation persisted until death only in 8 (Footnote 1. (a) p. 474). In attempting to understand this occurrence, the suggestion may be made either that the mechanism of the approach of death had nothing to do with the onset or persistence of this arrhythmia or that there is present in the mechanism of death a factor which inhibits a continuance of the irregularity. But in the latter case it would then be difficult to understand why auricular fibrillation was present until death in 8 cases. So far as its being rare except in the dying heart is concerned, it was possible to say "The fact that so many died without changes must be taken to mean that the proximity of death was not associated with the electrocardiographic changes on which we rely, even in those who had taken small amounts of the drug."<sup>1</sup>

Further observations have been made on changes in heart block during lobar pneumonia. The statement was formerly made<sup>1</sup> that, when digitalis was not given, although alterations in conduction occurred in both directions, the degree was not significant. A decrease, not greater than 0.06 second was observed in 11 patients and an increase, not greater than 0.03 second, in 4 patients. When digitalis was given, there was almost uniformly (80%) an increase of 0.04 second or more, leading in 7 instances to block. The patients were all in the febrile stage. Altogether 23 cases of heart block have been observed (Table 6), lesser grades of change in conduction have not been studied. It appears that 8 cases occurred during fever, but that in each case sufficient digitalis (or strophanthin) was given to bring about the arrhythmia. Reports of heart block in cases of lobar pneumonia have appeared in which this irregularity occurred during the febrile stage both with<sup>25,26,27</sup> and without<sup>28,29\*</sup> the administration of digitalis; cases have also been reported as occurring during the afebrile period of convalescence, again with<sup>29</sup> and without<sup>30†,31,32</sup> taking digitalis. The distinction between the febrile and postfebrile periods is sometimes not made<sup>33</sup> on the supposition that it is not important. Mention whether digitalis was given is sometimes omitted.<sup>34</sup> It is desirable to know the mechanism in those cases to which digitalis has not been given and in which block occurs after the subsidence of fever. Heart block appearing then apparently does not necessarily depend on taking digitalis.

\* There is no specific statement on whether digitalis was given.

† This was a case of influenza pneumonia.

**Summary.** An analysis of 1456 cases of lobar pneumonia has been made, to ascertain what influence the action of digitalis has on the course of this disease. Since the method of comparing treated and untreated cases by alternating them could not be applied, that of weighing the cases was employed instead. The reasons why, in a situation in which there are many unavoidably varied factors, this method is preferable to the other, have been given. In weighing the cases, factors which are untoward or unfavorable were first isolated and then by regarding the presence of each of them as having a value of one, the cases were grouped according to the number of their untoward factors. The importance of the untoward factors in determining the rate of mortality has been emphasized. It appears from the curve of mortality drawn according to the number of these factors that the rate depends on the number present. When the groups are studied in the light of whether digitalis was taken and also according to the size of the dose and the time in the course of the disease when it was administered, it appears that not giving digitalis, but the "severity of the disease" was the factor which decided the outcome. The action of digitalis is, in short, regarded as having no necessary influence on the processes of lobar pneumonia *per se*. When the inference that giving digitalis is harmful,<sup>2,3</sup> except perhaps in cases of auricular fibrillation, is compared with the one drawn in this study, it is suggested that the difference may be due to the difference in the methods of analysis employed. Attention is drawn to the fact that, in an unweighted analysis, so slight a difference, in a relatively small series, between treated and untreated patients as 7.7%, should have been found.<sup>2,3</sup> Finally, the effort has been made to ascertain whether digitalis is useful in auricular fibrillation or auricular flutter in which the action of digitalis may be expected to be beneficial; it appears that in those cases in which the outcome depends on safeguarding patients from the unfavorable effects of the rapid rate in auricular fibrillation and auricular flutter the administration of digitalis may be life saving.

Digitalis should not be regarded as an agent necessarily having an influence on the natural history of the pneumonic or pneumococcic infection.

**Conclusions.** 1. Giving digitalis does not seem to influence the course of events in lobar pneumonia.

2. Its action, in favorable cases, in which auricular fibrillation and auricular flutter occur, appears to be beneficial.

3. The outcome in lobar pneumonia depends on the "severity of the disease," which in turn depends especially on the presence of bacteriemia, the number of pulmonary lobes involved, and the existence of complications.

4. It is not certain whether the action of digitalis precipitates

the occurrence of auricular fibrillation. If it does so, the number of cases is small, especially in the earlier decades.

5. The proximity of death does not determine the onset of auricular fibrillation. Even when it was present, it ceased in 10 of 18 cases before exitus.

6. Heart block did not occur during the febrile period of lobar pneumonia except in those cases to which a sufficient amount of digitalis was given to bring it about.

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## PNEUMONIA IN UNDULANT FEVER.

## A REPORT OF THREE CASES.

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UNDULANT fever, like other generalized infections, may manifest itself as a localized diseased process in one or more of the various parts of the body. The occurrence of arthritis, endocarditis, bronchitis, nephritis, orchitis, peritonitis, meningitis and other localizations during undulant fever have been reported as recent contributions to the knowledge of brucelliasis although they have been described many years before chiefly by the British Army Surgeons in Malta. Pneumonia occurring during the disease has been only briefly referred to since the recognition of brucelliasis in the United States.

Fionentini<sup>2</sup> isolated brucella from the sputum of a case of Malta fever with pneumonia, and brucella were also isolated from the pus of a case of empyema. Eyre<sup>1</sup> in discussing 1000 cases of Malta fever due to the caprine variety of brucella noted the occasional occurrence of pneumonia and suggested that the pulmonary lesions were specific in nature. Vanni<sup>3</sup> described pneumonia produced in the guinea-pig by the inoculation of brucella and stated that grossly the lesions could not be distinguished from pulmonary tuberculosis at necropsy and described cases of undulant fever in men with bilateral apical infiltration similar to those of tuberculosis. All of these studies concerned the caprine variety of brucella.

Reports of pulmonary lesions occurring in patients infected with the bovine or porcine strains are rare and incomplete. Hardy<sup>7</sup> reported bronchitis in one-third of his cases and suggested that it was probably due to brucella. Pulmonary abscess occurred in one of his fatal cases. He also observed pulmonary lesions of a bronchopneumonic character in a high percentage of inoculated guinea-pigs and suggested that similar lesions may occur in man. Curschmann,<sup>4</sup> Kristensen and Holm,<sup>5</sup> Attinger<sup>6</sup> and others report cases of undulant fever in senile patients terminating with bronchopneumonia probably due to other organisms which are common invaders in debilitating diseases of the aged. Bjurström<sup>8</sup> reported a case of brucelliasis with bilateral bronchopneumonia and a pleural effusion from which brucella were isolated. The course of the disease and the character of the pulmonary lesions in Bjurström's case is very similar to the cases reported in this article. Puech and Vidal<sup>9</sup> isolated a brucella-like organism from the pleural fluid obtained from a case of undulant fever.

Because of the clinical similarities and frequent diagnostic difficulties arising between undulant fever, pulmonary tuberculosis and other lung diseases, it is especially important to recognize that pulmonary involvement occurs in certain cases of the former disease. The cases in this report were originally considered as cases of pneumonia rather than undulant fever because of the predominance of pulmonary signs and symptoms.

**Case Reports.** CASE 1.—R. T., a laborer, aged 55, began to notice marked fatigue about February 1, 1931, followed soon by chills, feverishness and drenching sweats. There were also severe joint pains, muscle soreness, backache and severe headache. The symptoms prevented the patient from working and at intervals necessitated bedrest for 2 or 3 days at a time. On April 12, he experienced severe lancinating pain in the lower left side of the chest aggravated by deep breathing and coughing. The cough soon became productive and as much as 8 ounces of serous mucoid sputum was raised daily. The development of pulmonary symptoms caused him to be sent to the hospital as a case of pneumonia on April 23.

On examination the patient was flushed, coughed frequently but appeared to be quite comfortable. There was slight cyanosis of the oral mucosa and finger nails. The expansion of the left lower side of the chest was diminished and posteriorly over this area there was a moderate impairment of resonance, increased tactile and vocal fremitus, high pitched breath sounds and an occasional coarse r le. The spleen was palpable.

*Laboratory Data:* Hemoglobin 78% (Sahli); 4,500,000 erythrocytes; 6000 leukocytes per c.mm., 70% of which were granulocytes and 28% lymphocytes. Several urine analyses were normal. The blood Wassermann reaction was negative. Agglutination tests on the serum showed complete agglutination of the brucella abortus antigen in a dilution of 1 to 160. Repeated examinations of the sputum for B. tuberculosis were negative.

Roentgen ray plates of the chest showed a diffuse increase of the bronchovascular markings and a triangular shaped area of diffuse haziness in the parenchyma of the left lower lobe near the periphery suggesting a chronic pulmonary fibrosis or a slowly resolving pneumonia. The temperature curve showed a daily afternoon elevation to around 38.9  C. (102  F.) associated with drenching sweats and chills or chilly sensations. The fever and the symptoms gradually subsided after 1 month of bedrest. The patient was discharged on May 30, afebrile, but with the signs of a slowly resolving parenchymal pneumonic lesion 7 weeks after its onset. Examination 6 weeks later, 13 weeks after the onset, showed that the lesion had entirely disappeared.

CASE 2.—J. J., a farmer, aged 41. Prior to the spring of 1932, 3 cows in his herd aborted. The patient drank as much as 1 gallon of raw milk from his herd daily. He became ill in August, 1933 and first noted malaise and disinclination for his usual work. After short rest period he felt fit again. During September, 1933 the patient became more fatigued and began to experience severe aches and lameness throughout the various muscles and joints. About September 24, while working in the field, he developed a chill which lasted several minutes. He went to bed, began to feel hot, and perspired so profusely that his bedding became wet. There was severe occipital headache. After 1 day he left his bed to oversee the farmwork but that evening again developed chills, fever and sweating. The aching of the joints became more severe. About October 8, following one of the chills, he developed a severe sharp pain in the right side of the chest aggravated by inspiration. He then developed a cough and raised a

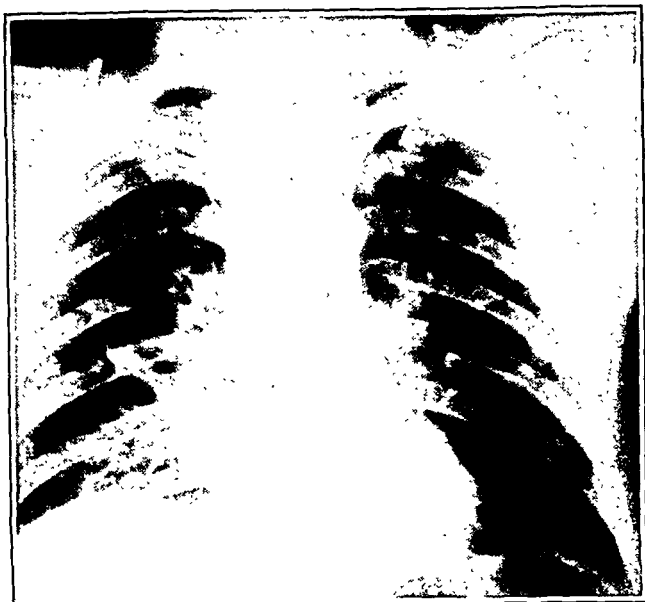


FIG. 1.—Case 2, taken 23 days after onset of pulmonary symptoms when lesion was most extensive, showing an area of diffuse density in the medial inferior portion of the right lung.

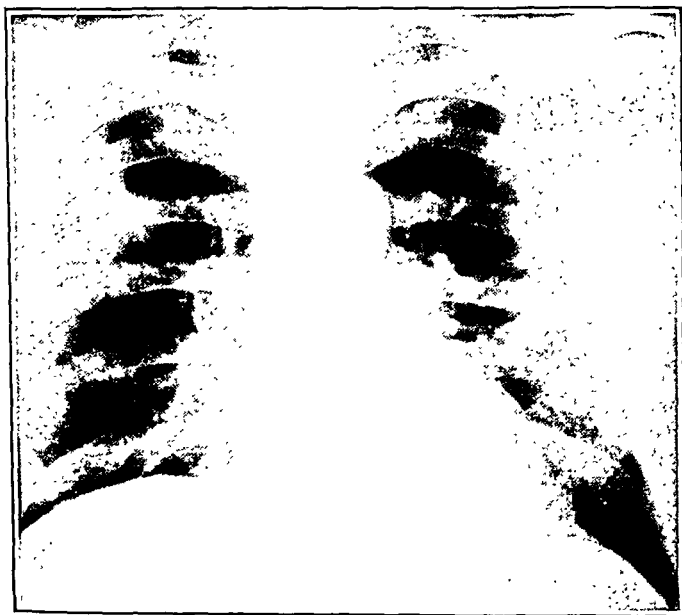


FIG. 2.—Case 3, taken 14 days after onset of pulmonary symptoms showing maximum involvement of lower portion of right upper lobe.



FIG. 3.—Case 3, taken 1 month after Fig. 2 showing some residue in lower portion of right upper lobe.

considerable amount of seromucoid sputum which later contained some bright red blood. The patient was hospitalized as a case of pneumonia on October 22. There was a weight loss of 30 pounds.

*Physical Examination:* He was flushed and only slightly toxic. He appeared to be quite comfortable in spite of a fever of  $40^{\circ}\text{C}$ . ( $104^{\circ}\text{F}$ .) and a respiratory rate of 26 per minute. The tongue was coated and moderately dry. There was impaired resonance, increased tactile and vocal fremitus, high pitched breath sounds and occasional râles over the posterior portion of the right lower lobe of the lung. The spleen was not palpable.

*Laboratory Data:* Hemoglobin 87%, 5,250,000 erythrocytes and 6000 leukocytes, 46% of which were lymphocytes. Urine normal; blood Wassermann test negative. The sputum was mucoid, tenacious and often contained bright red blood. On repeated examinations no tubercle bacilli were found. White mice and guinea pigs failed to become infected with pneumococci or brucella following injection with sputum. Agglutination tests for brucella abortus showed complete agglutination in dilution of 1 to 2560 and partial in 1 to 5120. The Mantoux skin test was negative and skin tests with heat killed brucella gave a moderately positive reaction. Three blood cultures were negative. A Roentgen ray plate of chest taken October 31, 1933 (Fig. 1) showed a diffuse increase of bronchiovacular markings suggesting a chronic non-tuberculous lung infection and a diffuse density in the medial inferior portion of the right lung suggestive of an unresolved pneumonia. Later roentgenograms showed some extension of the lesion but no change in its character.

Although fever was present each day it gradually diminished, and the patient improved slowly. By December 15, 15 weeks after the onset of his illness and 10 weeks after the development of the pulmonary symptoms, the patient had become afebrile and was discharged with some residual pulmonary infiltration in the right lower lobe. A Roentgen ray plate taken 4 weeks later showed that resolution had occurred.

CASE 3.—E. M., male, aged 61, a caretaker of small animals experimentally infected with undulant fever, complained of generalized aches and pains on October 27, 1933. November 1, he developed spells of weakness, headache, vertigo and profuse drenching night sweats and noticed some cough which produced a seromucoid sputum. These symptoms continued to come on in the late afternoon and evening. About December 1 he thought he was catching cold and felt worse. December 8 he felt hot and had sharp lancinating pain in the upper part of the right side of the chest with backache and headache. He continued to have fever and drenching sweats but no chills. He was forced to stop working on December 9. He reported to the Dispensary December 12 where his chest was examined but no abnormal findings were recorded. A Roentgen ray picture taken at that time showed a small area of increased density in lower portion of the right upper lobe. A lateral chest plate showed this lesion to be centrally placed. He was admitted to the hospital as a case of pneumonia on December 13. In spite of a temperature of  $39.2^{\circ}\text{C}$ . ( $102.5^{\circ}\text{F}$ .) the patient did not appear very ill.

*Physical Examination:* Several small cervical nodes were found. A few râles were heard at the level of the eighth spine posteriorly and about 2 inches to the right of the spine. The spleen was palpable, the heart showed a slight left ventricular hypertrophy. Blood pressure 190/96. Temperature  $37.78^{\circ}\text{C}$ . ( $100^{\circ}\text{F}$ .), pulse rate of 100, respiration rate 24.

*Laboratory Data:* The urine was negative on several occasions. Hemoglobin 78%, erythrocyte count 3,500,000, leukocyte count 8170 with a normal differential cell count. Agglutination test for Brucella abortus was complete in a dilution of 1 to 160. Blood cultures were negative. Wasser-



mann reactions were negative. Skin test with heat killed brucella gave an elevated indurated reddened area 1.5 cm. in diameter after 48 hours. Guinea pigs inoculated with sputum were negative.

While the patient was in the hospital the fever varied from 37.78° C. (100° F.) to 39.7° C. (103.4° F.) with an afternoon rise for 6 days, then slowly decreased followed by several exacerbations of above 37.78° C. (100° F.) for a period of about 2 months. The leukocytes count remained normal throughout the illness. Roentgen ray plates of the chest taken December 22, (Fig. 2) showed an increase in the size of the haziness previously noted during the first week. The shadow remained constant for about 2 months and slowly subsided. On January 20, 1934, there was still some residue of the pneumonic lesion, 17 weeks after its onset (Fig. 3). The patient was discharged on January 20, with a small residue of the pulmonary lesion and an occasional afternoon fever until February 1. A Roentgen ray plate taken March 2, showed the pulmonary lesions had entirely disappeared 4 months after the onset of the pulmonary symptoms.

**Comment.** These cases of undulant fever, each regarded as pneumonia when first seen, illustrate the error of focusing the attention to signs and symptoms confined to the lungs. Careful history, physical examination and laboratory studies revealed the pulmonary lesion to be merely part of the general infection. The 3 cases had several features in common, namely, a period of several weeks of mild illness before the onset of pneumonic symptoms, none were very ill at any time, not as ill as one would expect with pneumonia due to other organisms. The pulmonary lesions in each were atypical, according to physical signs and Roentgen ray studies and required from 13 to 17 weeks for complete clearing. In all cases an attempt should be made to determine whether the pneumonia is due to the brucella or to the more commonly encountered organisms which invade individuals whose resistance has been reduced by the disease in question. This is often impossible to decide unless there occurs opportunity for lung puncture or necropsy study. Bacteriologic proof of the specificity of the pneumonia was not possible in our cases since all patients recovered and brucella were not cultured from the sputum. The pneumonia was considered as probably due to brucella.

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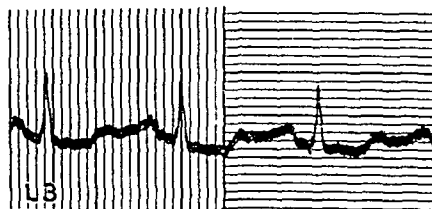
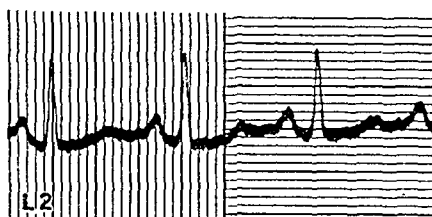
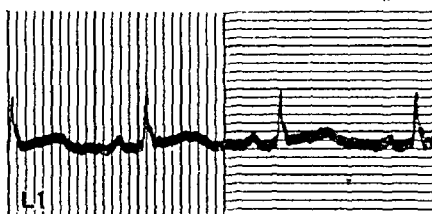
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# VALUE OF SERIAL ELECTROCARDIOGRAMS IN CORONARY THROMBOSIS.\*

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THE not infrequent failure of a single electrocardiogram to show coronary thrombosis in cases having a history of a prolonged anginal syndrome, with dyspnea, epigastric distress, fall in blood pressure, fever, leukocytosis, perhaps pericardial friction and even positive autopsy findings, has unfortunately detracted from the true value of this method of examination.<sup>1, 2, 3</sup>

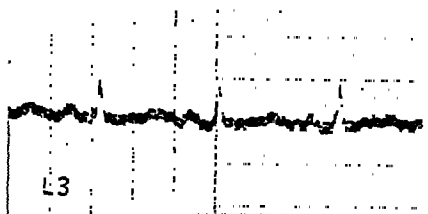
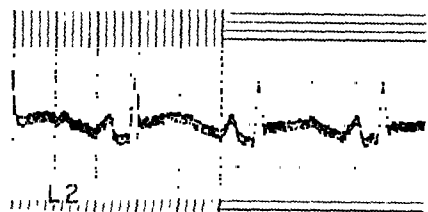
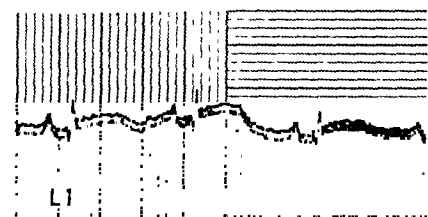


Series "A," No. 1. Twelve hours after onset of typical symptoms of coronary thrombosis, illustrating the cove-shaped  $T_1$  with reciprocal  $T_2$  and prominent  $P_2$ . Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

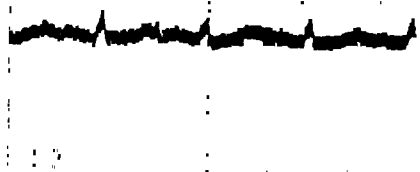
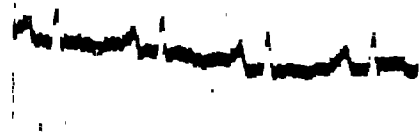
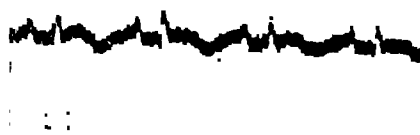
Since a coronary accident gives rise to a series of variable changes in each individual heart, depending largely upon the degree of collateral circulation, the location and size of the occluded vessel and other factors whose relationship is less well understood, such

\* Read before the 18th Annual Clinical Session of the American College of Physicians, in Chicago, April 16, 1934.

as the chemical and physical reactions of the blood and tissues, the platelet count, and so forth, so the electrocardiographic curves in turn show considerable diversification.<sup>4, 5</sup> When a large vessel is suddenly obstructed, with insufficient collateral circulation, we may expect an early injury current, showing *one* of the forms of the characteristic coronary curves. In other instances, where a tiny twig is occluded, with a good collateral circulation, the patient may experience a prolonged anginal syndrome without showing any



No. 2.



No. 3.

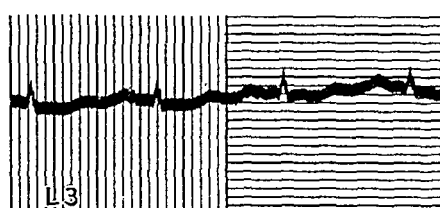
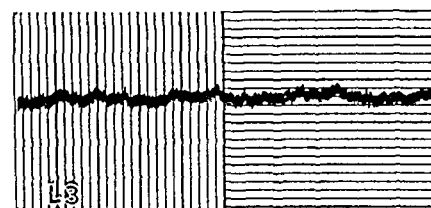
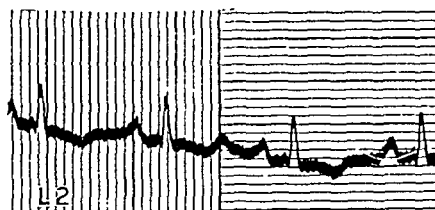
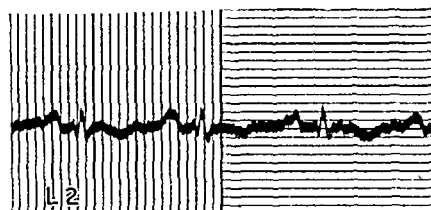
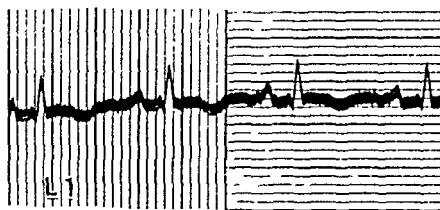
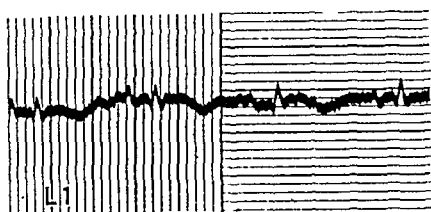
Series "A," No. 2. Two days following "A"1, showing the elevated  $R-T_1$  and  $_2$  with prominent  $P_2$ , and lowered voltage. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "A," No. 3. Twenty-six days following "A"2, showing marked decrease in voltage, with inverted  $T_1$ . Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

variation in the electrocardiogram. Where a gradual thrombosis takes place, correspondingly gradual changes in the electrocardiographic records may be found, or there may be no change until the occlusion is complete, thereby giving only late variations, the characteristic curves being delayed for a week or more. In others, where the initial insult has been the occlusion of a small branch, with good collateral circulation, a positive curve may appear early and rapidly revert to normal limits. Should some of the collateral

circulation in turn be occluded, the characteristic positive form may again become manifest.

Priest and Saphir have demonstrated the autopsy findings of patients who have had coronary thrombosis without infarction who later developed infarction in the area supplied by the original occluded vessel following thrombosis of vessels supplying collateral circulation to this part.<sup>6</sup> As pointed out by Willius,<sup>5, 7</sup> and Fowler



No. 4.

No. 5.

Series "A," No. 4. Fourteen days after "A"3—a further decrease in voltage, with prominent  $P_2$  persisting. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "A," No. 5. Eleven days following "A"4, demonstrating an increase in voltage, with recovery. (The Series "A" demonstrating the changing EKG of coronary thrombosis.) Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

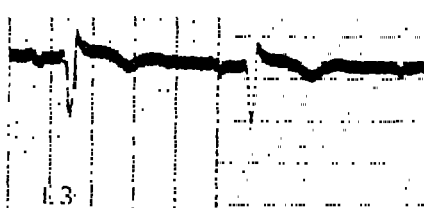
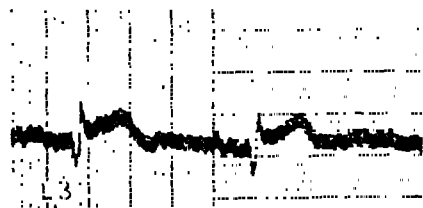
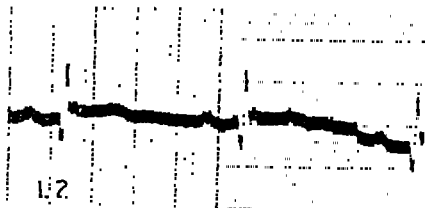
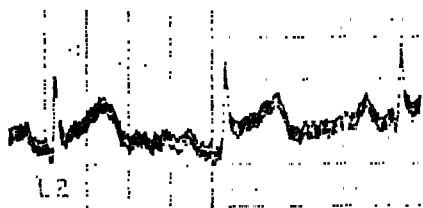
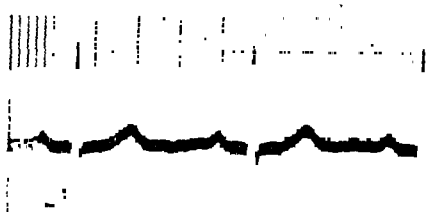
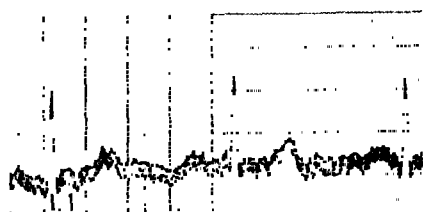
and Smith,<sup>8</sup> the attack may consist of a series of coronary thromboses.

And so, many conditions may alter the simple sequelæ of an obstructed coronary vessel, at times giving electrical potentials resulting in unusual and atypical curves. The most conclusive evidence is obtained by reviewing a series of electrocardiograms, keeping a watchful eye for the characteristic changes of coronary thrombosis. These signs are now well known and comprise:

(a) The elevation and depression of the  $R-T$  intervals, with at times reciprocal changes in Leads I and III.<sup>9, 10</sup>

(b) Cove-shaped Pardee  $T$  waves,<sup>11</sup> with later inversion of the terminal portion and conversely the sharply upright  $T$  wave the exact opposite of the "Pardee-wave," with elevation of the  $R-T$  interval, as described by Bohning and Katz.<sup>12</sup>

(c) The low voltage of the  $Q-R-S$  complexes, as emphasized by White<sup>13</sup> and Wearn.<sup>14</sup>



No. 1.

No. 2.

Series "B," No. 1. Illustrating the high take-off of  $T_2$  and  $s$ , three hours after the onset of a coronary accident. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "B," No. 2. Twenty-four hours later, showing a decrease in the height of the  $T$  take-off in Leads II and III, with a flattening of  $T_2$  and terminal inversion of  $T_3$ . Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

(d) The deep  $Q_3$  following the criteria of Pardee.<sup>15</sup>

(e) Prominent  $Q_1$  and  $Q_2$ , described by Wilson and others.<sup>16</sup>

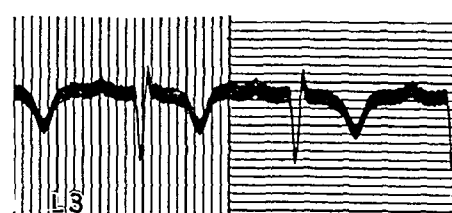
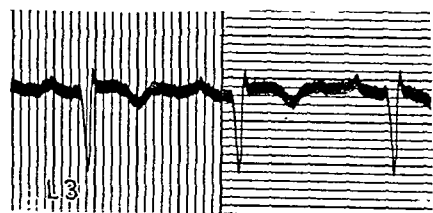
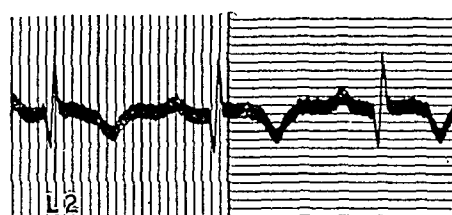
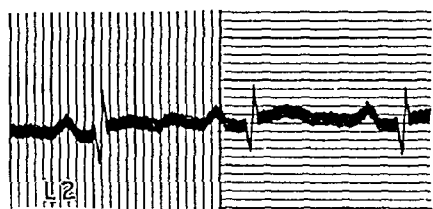
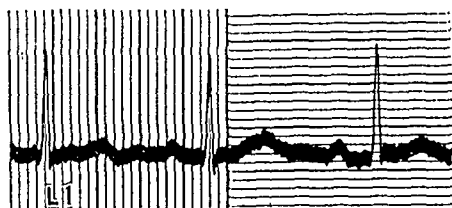
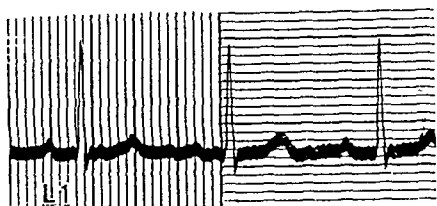
(f) The upright or diphasic  $T$  waves in the chest leads, with displaced  $R-T$  intervals, according to Wood *et al.*<sup>17</sup>

(g) Prominent  $P$  waves of Masters,<sup>18</sup> and

(h) Equally important and more constant than all the foregoing findings, variations in the serial curves themselves, as emphasized by Herrick,<sup>4</sup> Cooksey and Freund,<sup>3</sup> Oille,<sup>19</sup> and others.<sup>20</sup>

Hurxthal reports a case in which  $T_1$  was inverted 6 days before the attack and became upright 1 hour after the accident.<sup>1</sup>

In reviewing a series of 72 cases where serial curves were obtained only 2 failed to show significant changes.\* One occurred in a physician of 35 with typical history and findings, including pericardial friction, fever, leukocytosis, with prostration and stenocardia at the



No. 3.

No. 4.

Series "B," No. 3. Forty-eight hours following "B"2, showing a further inversion of  $T_3$ , with  $R-T_2$  and  $s_3$  approaching the isoelectric line. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "B," No. 4. Ten days after  $B_3$ , showing deep inversion of  $T_2$  and  $s_3$ , with slight elevation of  $R-T_2$  and  $s_3$ . (Series "B" illustrating the changing EKG of coronary thrombosis.) Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

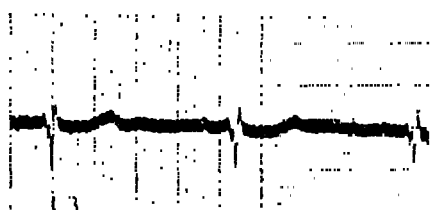
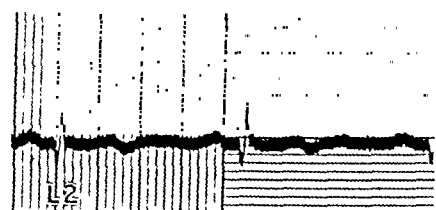
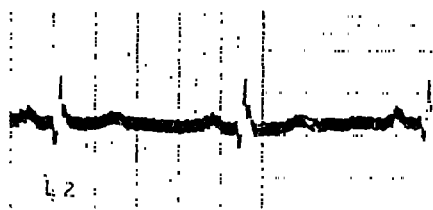
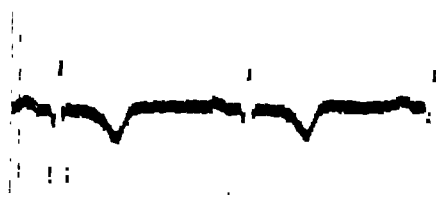
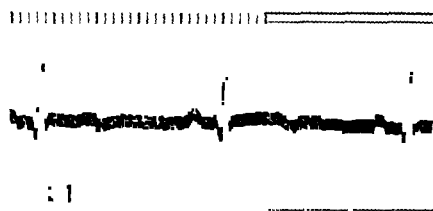
onset. The other was in a physician in the sixties, who showed only a slight flattening of the  $T$  wave. A series of 6 serial curves were obtained in the first case, over a period of 3 months, and a series of 7 in the second case, over a period of a year. So, at times, confirmatory evidence may be seen in a normal curve where the  $T$  wave was previously inverted, or there may be only a flattening or inversion of a previously upright  $T$  wave. Six cases of the present series with 3 or more serial records displayed a slight inversion of

\* Records of St. Francis Hospital (Evanston), Evanston Hospital, Swedish Covenant Hospital, Chicago, and private patients.

$T_1$  or  $T_1$  and  $T_2$ , occurring from the 10th to the 18th day; 3 showed changing arrhythmias, with no characteristic alteration in the  $T$  waves or  $R$ - $T$  intervals.

Cooksey and Freund have studied 24 cases with serial curves, showing 100% positive findings.<sup>3</sup>

Pardee<sup>21</sup> reports 25 cases at the New York Hospital which had almost daily records, showing positive findings in at least one record



No. 1.

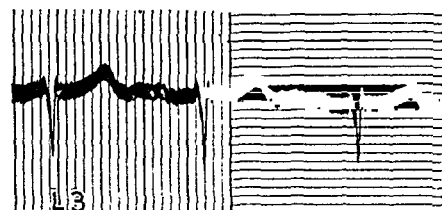
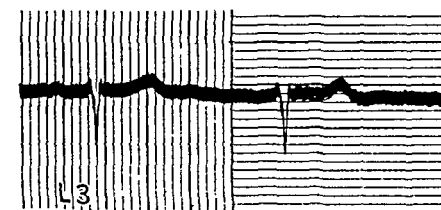
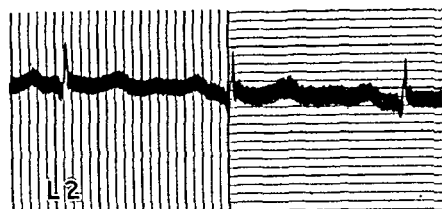
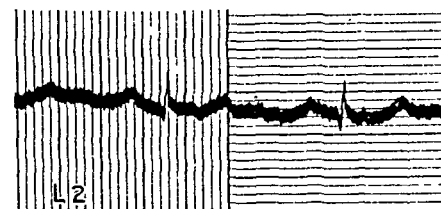
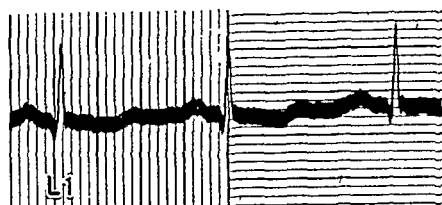
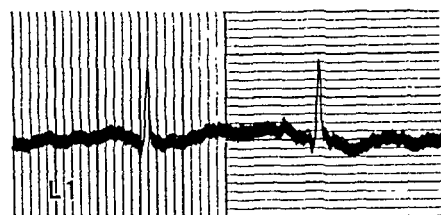
No. 2.

Series "C," No. 1. Forty-eight hours following a coronary accident, showing prominent  $Q_1$  and  $2$ , with cove-shaped  $T_1$ , slightly increased  $R$ - $T_2$ , and  $T_3$  reciprocal of  $T_1$ . Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "C," No. 2. Twenty days after "C"1, showing marked inversion of  $T_1$  with reciprocal upright  $T_3$ , inversion of  $T_2$ , and decreased voltage of  $Q$ - $R$ - $S$ , all leads. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

in all the patients. Oille reviewed 200 cases from the records of Toronto General Hospital in which only 2 or possibly 3 showed no significant signs. He cites 2 cases which showed significant changes 2 days before the pain and clinical onset.<sup>22</sup> Kelly also noted a case at Cook County Hospital where a routine electrocardiogram was taken, showing positive signs of coronary occlusion, with the clinical attack of pain, cardiac failure, fever and leukocytosis occurring 24 hours later.<sup>23</sup>

Coronary occlusion curves may be simulated by those found in other conditions, such as chronic valvular disease, active rheumatic infection,<sup>24</sup> influenza,<sup>25</sup> diphtheria,<sup>26</sup> pneumonia,<sup>27</sup> hyperthyroidism, pericarditis with effusion, uremia, and certain drug poisonings, such as digitalis,<sup>28</sup> quinidin and emetin. The hearts of athletes, probably hypertrophied, but usually showing teleradiograms within normal limits, occasionally give suggestive elevations and depressions of



No. 4.

No. 5.

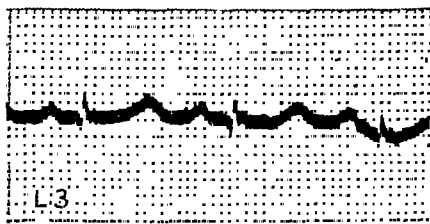
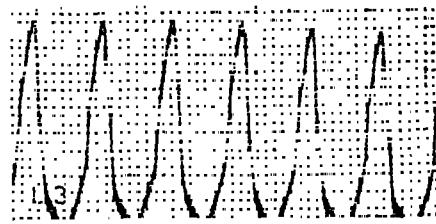
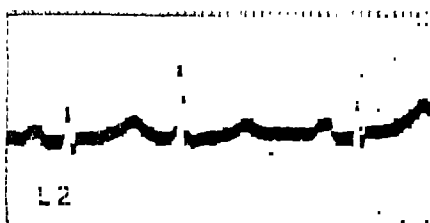
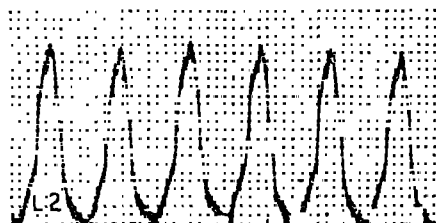
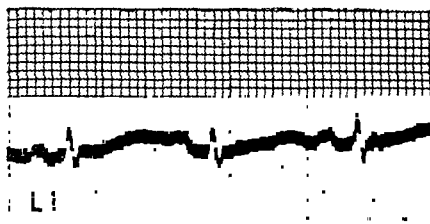
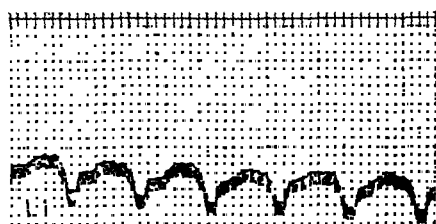
Series "C," No. 4. Twenty days following "C"3, showing increased voltage, with  $T_1$  approaching the isoelectric line. Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

Series "C," No. 5. Forty-eight days following "C"4, showing practically isoelectric  $T_1$  and decrease in the voltage of the upright  $T_s$ . (Series "C" illustrating the changing EKG of coronary thrombosis.) Lead No. 1—between right and left arms; Lead No. 2—between right arm and left leg; Lead No. 3—between left arm and left leg.

the  $R-T$  intervals resembling one of the forms seen in coronary thrombosis. Some of the coronary forms have been simulated by placing the patient with a normal heart in unusual positions.<sup>29</sup> Serial curves in coronary thrombosis will rule out simulating curves of other conditions which are constant in form, such as those of chronic valvular disease, the hypertrophied hearts of athletes, chronic coronary disease (as the curves in coronary sclerosis), and in some cases of thyroid disease, as in the case of Dr. C., who showed



a persistent bundle-branch block for 2 years, returning to normal following the removal of a substernal thyroid tumor. In the case of active infection and drug intoxication where serial curves may show change from day to day, the findings in the coronary waves



No. 1.

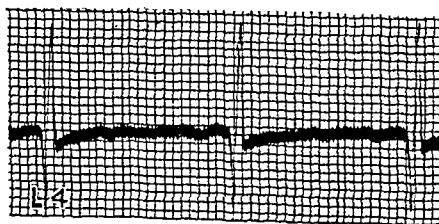
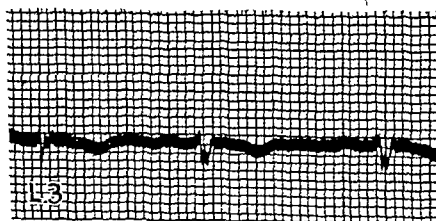
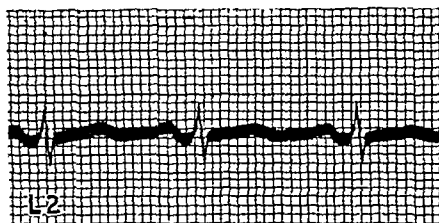
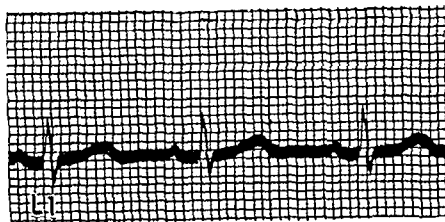
No. 2.

Series "E," No. 1. Twelve hours after onset of thrombosis, showing ventricular tachycardia.

Series "E," No. 2. Three days following "E"1; heavy quinidin therapy, showing low voltage; nodal extrasystole Lead II, increased  $R-T_3$  and sharply upright  $T_4$ .

are usually more characteristic and very infrequently lead to a faulty diagnosis. Careful correlation of the electrocardiogram with the clinical history and findings is, of course, always advisable and often essential.

The more frequently electrocardiograms are taken the more evidence will be obtained. From a practical standpoint it is desirable to obtain the information early and take the minimum number of records; it is suggested, therefore, that a curve be taken as soon after the accident as possible, followed by another the following



Series "E," No. 4. Showing inverted  $T_3$ , isoelectric  $T_4$ , with upright  $T_1$  reciprocal of  $T_3$ . (The series "E" demonstrating the changing EKG of coronary thrombosis.)

In Series "E," Lead IV is taken through chest with right arm electrode anterior over cardiac apex and left arm electrode posterior between angle of scapula and vertebral column.

day, with a third curve 48 hours after the second, and further curves, if necessary, at weekly intervals for a month or longer. If these serial records are obtained the accuracy of the electrocardiographic examination in coronary thrombosis will closely approach that of the Wassermann and Kahn tests in syphilis.

**Summary and Conclusions.** An attempt has been made to show the value of serial curves in the diagnosis of coronary thrombosis.

1. It is possible for single records to be taken at times when characteristic signs of coronary thrombosis are absent.

2. The serial records are usually characteristic and rule out those conditions simulating coronary occlusion curves in a single record, such as seen in chronic valvular disease, hypertrophied hearts of athletes, and those of chronic coronary disease.

3. The serial curves of acute infectious diseases usually are not characteristic enough to confuse the diagnosis. In an occasional case it may be necessary to rely upon the correlation of the clinical history and findings with the electrocardiogram.

4. The time of taking these curves for practical purposes has been suggested, *i. e.*, as soon as possible after the accident; then, the next day; 48 hours after the second; and, if necessary, at weekly intervals for a month or longer.

5. It may be that chest leads will further increase the accuracy of serial curves. In our experience the fourth lead has been more sensitive to digitalis than the conventional leads.

6. In 72 cases of coronary thrombosis where serial curves were taken only 2 failed to show significant changes.

7. Serial curves of 4 cases are shown.

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## OBSERVATIONS ON THE EFFECT OF AN ARTERIOVENOUS FISTULA ON THE HUMAN CIRCULATION.

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AN arteriovenous fistula causes profound changes in the circulation. The condition is not uncommon and its clinical characteristics are now well recognized. Adequate study, however, has been limited to relatively few cases and for that reason the mechanism of many of its effects is still controversial. Further investigation may be expected not only to clarify the phenomena associated with arteriovenous communications, but also to throw light upon related conditions in the cardiovascular system. The following observations are therefore reported which were made upon a case exhibiting the characteristic effects of a traumatic fistula between the left femoral artery and vein.

Nicoladoni<sup>17</sup> in 1785 first described the fact that occlusion of an arteriovenous fistula by digital compression is followed by a marked slowing of the pulse rate, the so-called bradycardiac reaction or Branham's sign.<sup>20</sup> Subsequent studies have shown that this is associated with a rise of arterial blood pressure upon which it is believed to depend. Other effects of such a fistula include an increase in the total blood volume, a decrease in the systemic capillary blood flow, generalized arteriolar dilatation and many of the peripheral signs of aortic regurgitation. The effect on the heart itself is the production in the majority of cases of a striking degree of enlargement. Progressive circulatory insufficiency is the rule in the presence of a fistula of significant size involving a large artery.

In the treatment of aortic aneurysm, end-to-end anastomoses have been established between artery and vein apparently without untoward effect.<sup>1,26</sup> Since the present case exhibited a fistula of the lateral type, the conclusions reached in this study do not necessarily apply entirely to other forms of arteriovenous communications, either surgical or congenital.<sup>23</sup>

**Case Report.** D. W., a colored male, aged 35, and a laborer by occupation, was admitted to the Philadelphia General Hospital on June 4, 1934, complaining of shortness of breath and swelling of the legs. He stated that he had been in good health until 5 months previous, at which time he had been accidentally shot, a 0.38-caliber bullet entering his left groin. He remained for 8 days in a local hospital during which time his left leg became swollen. On returning home he first noticed a buzzing sensation beneath the site of injury. He returned to work, but found that both

legs then began to swell. He was short of breath and fatigued by slight effort. The symptoms gradually increased in severity and were accompanied by attacks of faintness, palpitation and precordial pain. He became unable to sleep in a recumbent posture and awoke to urinate several times nightly. Occasionally the urine appeared red. Rest at first caused subsidence of the swelling and dyspnea, but the symptoms ultimately became so severe that he was forced to give up his work and come to the hospital. The patient was married, had no children and indulged in alcohol to excess. The family history was negative for cardiovascular renal disease and the past medical history was irrelevant.

*Physical examination* revealed a well-developed colored male with marked edema of both legs. The temperature was 99°, respiratory rate 20, pulse rate 80 and blood pressure 140/80. Cyanosis was not evident. The tendon and pupillary reflexes were normal. The head showed no significant abnormality. Examination of the lungs showed evidence of passive congestion. The heart was greatly enlarged to percussion, the borders being 14 cm. to the left of the midline, and 5 cm. to the right. The rhythm was regular, the sounds clear and no murmurs were heard. The liver was slightly enlarged. There was no definite ascites. In the left groin there was a scar of a bullet wound, and over the upper femoral sheath a pulsating mass about the size of a walnut could be felt. Over the mass there was a well-marked systolic thrill and a bruit which was continuous but louder during systole and transmitted down the leg. Both legs were cold and exhibited pitting edema, more marked on the left side which also had a somewhat darker color. The radial arteries were not sclerosed. The pulses were full and equal and there was slight capillary pulsation visible beneath the fingernails.

Firm digital pressure on the mass in the left groin caused a disappearance of the bruit, a rise of blood pressure from 140/80 to 170/120 and a slowing of the pulse rate from 80 to 50.

Blood count showed 100% Hb., 5,000,000 R. B. C. and 5000 W. B. C. Urinalysis and blood chemistry were normal. Blood and spinal fluid Wassermann tests were negative. Teleroentgenogram showed marked passive congestion of both lungs and a greatly enlarged heart, the transverse diameter being 19.5 cm. to a chest diameter of 30 cm. (Fig. 1a).

*Diagnosis.* Traumatic arteriovenous aneurysm of the left femoral artery and vein with secondary cardiac dilatation and congestive failure.

*Course.* The patient was confined to bed with no essential medication from June 4 to June 14 and thereafter allowed up at will until operation, on July 13. On June 26, fluoroscopic examination showed that the transverse diameter of the heart was reduced to 16.4 cm., which value was found again on July 6. The edema of the legs persisted, especially on the affected side, but was much reduced. It was maximal in the evening and tended to subside with rest in bed.

*Operation* was performed on July 13, by Dr. P. A. McCarthy. Under N<sub>2</sub>O-ether anesthesia, an incision was made exposing the left common iliac artery and vein and the deep and superficial femoral vessels. The aneurysm was enveloped in dense scar tissue, measured approximately 1½ by ¾ in., and involved the common femoral vein with a fistula from the common femoral artery. With hemostasis obtained by tapes about the common iliac and femoral arteries and veins, the aneurysm was cut free from the artery to which it was attached for a distance of about 1 in. The fistula so disclosed measured ¼ in. in diameter. The openings in the artery and vein were closed by suture with fine silk. Removal of the tapes showed free blood flow, although the peripheral segment of the artery appeared much contracted. A layer of fascia was inserted between the artery and vein and

the wound closed. Pulsation in both the femoral and dorsalis pedis arteries was palpable.

*Further Course.* Except for occasional vague pains in the affected leg, there were no postoperative complications. The pulse rate remained between 70 and 100 for the first 3 days and thereafter between 60 and 80. The edema disappeared entirely from both legs. Teleroentgenogram, on August 2, showed the complete disappearance of pulmonary congestion and the transverse diameter of the heart was reduced to 12.5 cm., a value well within normal range.

The patient was discharged on August 6. From that time until his last visit, on September 18, he had no complaints other than a sensation of warmth and occasional numbness in the affected leg. The heart size remained unchanged to fluoroscopic examination. There was, however, a slight pitting edema of the affected leg where pulsation was no longer palpable in the femoral and dorsalis pedis arteries. The resting blood pressure in the arm was 130/84, with a pulse rate of 70. In the right leg the blood pressure was 150/80, with an oscillometric index of 3.5, but in the left leg the blood pressure was 85/50, with an oscillometric index of 1.5. The patient had resumed his work as a laborer.

**Results.** The patient was studied over a period of 6 weeks before and 8 weeks after operation. The following observations were made.

*Arterial Blood Pressure.* Many determinations of the resting but non-basal arterial tension measured by the usual auscultatory method gave values of 140 to 156 mm. Hg. for systolic pressure and 77 to 96 for diastolic pressure. Digital compression of the aneurysm sufficient to cause disappearance of the bruit produced a consistent rise of both the systolic and diastolic levels, the former to pressures between 150 and 190 and the latter between 115 and 130 mm. Hg. After operation systolic pressure averaged 110 to 140 and diastolic pressure 70 to 84 mm. Hg. The arterial pressure under basal conditions showed less variation, the mean values being 126/62 with the fistula open, 127/81 with the fistula occluded and 119/78 after operation.

The effect of an arterial leak with diminution of the peripheral resistance is to cause a lowering of blood pressure, most marked in diastole. In the present case, however, the non-basal blood pressure was usually higher with the fistula open than after operative closure. Under basal conditions the low diastolic level was partly compensated by an increased pulse pressure. This fact is of importance since a diminished coronary blood flow in arteriovenous fistula has been attributed to a low perfusion pressure in the aorta.<sup>18</sup> Actually the mean pressure remained well within what are considered to be the normal physiologic limits. As to the sudden rise of blood pressure on digital occlusion of the fistula there is no reason to suppose that it is other than a purely hemodynamic effect of an increased peripheral resistance.<sup>7,18</sup>

The use of an optical oscillometer permitted the estimation of both end and lateral pressures.<sup>3</sup> These determinations were made under basal conditions. The average difference between end and

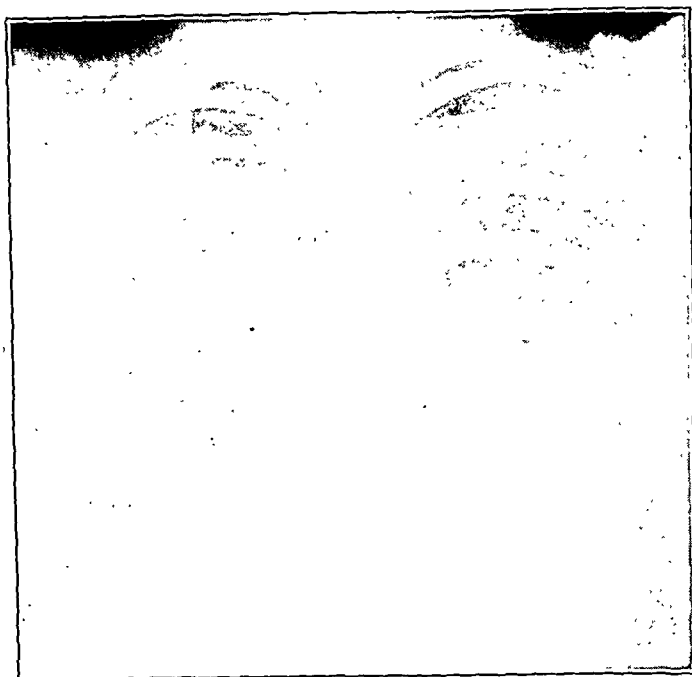
lateral pressure in diastole did not exceed 5 mm. Hg. and was relatively negligible. The systolic end pressure, however, exceeded the corresponding lateral pressure by 17 mm. Hg. On occlusion of the fistula, both by compression and operation, this difference was reduced to 8 mm. Hg. or one-half of its former value. The phenomenon is attributable to the increase in velocity of systolic expulsion in the presence of an arterial leak. It is similar in cause to the relatively greater difference between end and lateral pressure found in the presence of aortic insufficiency where an increased proportion of the arterial pressure takes the form of kinetic energy.<sup>2</sup> The degree of increase in the difference between end and lateral blood pressure due to arteriovenous fistula is particularly interesting since it is on account of this lowering of the lateral pressure that surgical arteriovenous anastomosis has been used in the treatment of aortic aneurysm.

A few measurements of blood pressure were made on the femoral artery under non-basal conditions. On the normal leg the average pressure with the fistula open was 224/118, increasing to 300/170 when the fistula was compressed. In the artery below the fistula, the systolic pressure rose from 193 with the fistula open to 230 on compression. After operation, blood pressure in the normal leg approximated the brachial value at 155/80 while in the operated leg, due probably to the narrowing of the sutured artery, the pressure measured only 85/50.

*Pulse Rate.* The bradycardiac reaction, consisting of slowing of the pulse rate on compression of an arteriovenous fistula, was well exhibited. The average pulse rate was 70 to 100 per minute with the fistula open. Digital compression of the fistula caused a slowing of the rate to 48 to 60 with a prompt return to the former values when the pressure was withdrawn. The pulse rate after operation was significantly slower and averaged between 52 and 84.

The bradycardiac reaction may be completely abolished by full doses of atropin,<sup>18</sup> a procedure which was not attempted in this case because of the advanced degree of circulatory insufficiency. On account of the effect of atropin, the slowing of the pulse rate on occlusion of the fistula is believed to be dependent upon the coincident rise in blood pressure.<sup>14,18</sup> It is interesting to note, therefore, that the degree of bradycardia is not always proportional to the change in blood pressure. An example will suffice. On one occasion compression of the fistula caused a rise of blood pressure from 144/80 to 160/120 and the pulse rate slowed from 80 to 50. With release of compression, blood pressure fell to its former level while the pulse rate increased to 84. On a second occasion compression of the fistula caused a rise of blood pressure from 110/65 to only 125/82 while the pulse rate again fell from 82 to 50. On release of compression the systolic pressure remained unchanged while the diastolic level dropped only 10 mm. Hg. to 72. Even this slight

*a*



*b*

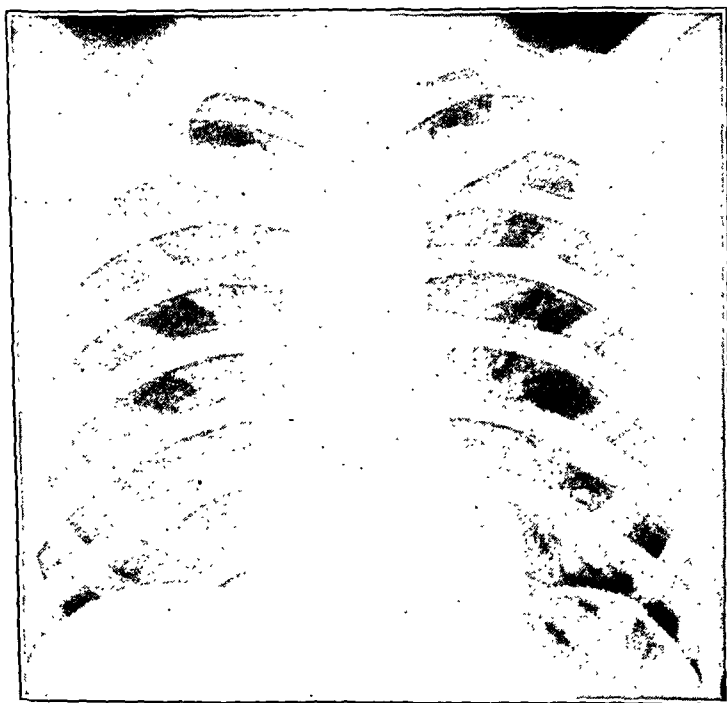


FIG. 1.—Teleroentgenogram of heart; *a*, taken 6 months after establishment of traumatic arteriovenous fistula; *b*, taken 3 weeks after operative obliteration of the fistula.





change in blood pressure, however, was accompanied by the usual increase in pulse rate from 54 to 82. In other words, equal degrees of change in pulse rate were associated with widely different degrees of change in blood pressure. Such evidence may be interpreted as indicating that the bradycardiac reaction does not depend exclusively upon the absolute height of the blood pressure, but is modified as well by other factors, including the cardiac output.

*Venous Pressure.* The venous pressure was not determined on admission but the degree of pulmonary congestion and peripheral edema at that time indicate that it was probably above normal. Prior to operation when the signs of congestive failure had largely disappeared, measurements of venous pressure were made by direct cannulation of the antecubital vein. Blood rose in an L tube to an average height of 75 mm. above the estimated heart level.<sup>6</sup> When the column of blood reached a constant level, digital compression of the fistula caused an average fall of 13 mm. After operation, the venous pressure, similarly measured, averaged 55 mm. above heart level.

It is often stated that the venous pressure is abnormally high in the presence of an arteriovenous fistula.<sup>20</sup> Lewis and Drury believe that in the absence of congestive failure this is not necessarily or even customarily true.<sup>18</sup> Observations on the present case indicate that the pressure in the peripheral veins was not above normal limits but was relatively increased by the fistula. It is questionable whether the observed pressure changes correspond exactly to changes in the right auricular pressure. If they do, the slightly higher value with the fistula open may depend upon an increase in the total venous return flow. On the other hand, the pressure in the brachial veins may not present quantitatively the values in other parts of the venous system. In any event, the alteration in venous pressure at the right auricle must have been relatively slight.

*Respiration.* The average respiratory minute volume at rest was 7.8 liters with a respiratory rate of 18 per minute. On compression of the fistula, these values fell to 7.3 and 17 and after operation to 6 and 16 respectively. The increased respiration probably depends upon a slowing of cerebral blood flow, but the change is seldom conspicuous.<sup>18,24</sup>

*Skin Temperature.* Estimations of skin temperature were made with a thermocouple and readings were obtained from the thigh, calf, dorsum of the foot and second toe of both legs. The average temperature was slightly higher in the leg having the aneurysm than in the normal leg, a phenomenon previously recognized.<sup>5,14,16</sup> On compression of the aneurysm for 10 minutes there was a rise of temperature in both legs which was greater on the normal side. The maximum rise was 0.85° C. in the affected leg and 1.45° in the normal leg.

Changes in skin temperature are probably not directly proportional to changes in total blood flow, but the values obtained indicate at least that there was a definite increase in capillary circulation through both legs when the fistula was occluded. They confirm other evidence that in the presence of arteriovenous fistula, the blood flow may be considerably diminished even in regions distant from the lesion and even in the presence of a compensatory increase in cardiac output.

*Cardiac Output.* The cardiac output was measured under basal conditions by the modified ethyl iodid method<sup>25</sup> and by the acetylene method. With the fistula open the minute volume averaged 5.15 liters making a cardiac index of 2.64. A reduction of 20% occurred on compression of the fistula, the minute volume falling to 4.13 liters and the cardiac index to 2.12. After operation the minute volume fell to 3.91 liters and the cardiac index to 2.02, making a total reduction of 24%.

The output of the heart per beat (calculated from the minute volume) averaged 65.7 cc. at a pulse rate of 78. On compression of the fistula the output per beat increased to 75.8 cc. with slowing of the pulse rate to 53. After operation the average output per beat was 68.5 cc. at a pulse rate of 56.

An increased minute volume in the presence of an arteriovenous fistula has been reported clinically<sup>5,15,24</sup> and in the experimental animal.<sup>9,10,11,19</sup> Although Lewis and Drury<sup>18</sup> conclude that in arteriovenous fistula "the output of the heart does not appear to be usually altered," the present case supports the clinical and experimental evidence that an increased minute volume is a compensatory mechanism of great constancy whenever the leak is of significant size and the heart is still sufficiently competent. The changes in stroke volume in clinical cases reported elsewhere in the literature are variable. In the case reported by Smith<sup>24</sup> there was a reduction of 65% after operation, while Ellis and Weiss<sup>5</sup> found, as in the present case, very little change after operation but a significant increase as an immediate effect of occlusion. The increased minute volume appears, therefore, to depend largely upon an increased pulse rate rather than upon changes in stroke volume.

*Heart Size.* Teleroentgenogram on admission showed an advanced degree of pulmonary congestion and a hugely enlarged heart (Fig. 1a) the silhouette of which measured 194 sq. cm. with a transverse diameter of 19.5 cm. The heart to chest ratio was 65%. Four weeks later, 10 days before operation, the area of the silhouette by orthodiagram had decreased to 141 sq. cm. and the transverse diameter to 16.4 cm. The patient had received no digitalis or other significant medication so that the change is presumably an effect of rest alone. Three weeks after operation the cardiac silhouette by orthodiagram measured 108 sq. cm. and the transverse diameter 12.5 cm. with a heart to chest ratio of 42% (Fig. 1b). No further

change has been noted on subsequent examinations. The total reduction of the cardiac silhouette and transverse diameter was 45%.

On fluoroscopic examination prior to operation it was found that digital occlusion of the fistula caused a decrease in size of the heart shadow from 141 sq. cm. to 126 sq. cm. and of the transverse diameter from 16.4 cm. to 15.2 cm. Other observers have reported either increase<sup>5</sup> or decrease<sup>22</sup> in heart size under similar circumstances. It seems likely that the direction of change is inconstant since it is a resultant of several variable factors including venous return, heart rate, arterial blood pressure and the degree of cardiac dilatation already present.

*Pulmonary Blood Volume.* A phenomenon which does not appear to have been previously described is the visible change in pulmonary blood volume incident to sudden opening and closing of the fistula. Under fluoroscopic examination, digital compression of the aneurysm was followed by a prompt and consistent increase in translucency of the lung fields which diminished on reopening of the leak. The procedure was repeated and the effect confirmed by several observers. The change in translucency of the lung fields may be explained by a change in pulmonary blood volume on sudden diminution of the venous return. It probably represents a shift of blood from the venous and pulmonary bed to parts of the arterial and capillary system inadequately filled because of the short circuit at the fistula. The observation is of particular interest in view of the unexplained lowering of pulmonary resistance found by Gibbon and Churchill<sup>9</sup> in experimental arteriovenous fistula. It also affords further evidence of the blood reservoir function of the lungs to which Hochrein and Keller<sup>13</sup> have recently called attention.

*Oxygen Consumption.* The oxygen consumption averaged 247 cc. per minute on repeated determinations before operation, both with the fistula opened and closed. The basal metabolic rate was - 8.1%. After operation the oxygen consumption was 265.7 cc. per minute or 0.5% of the calculated value. The change is too slight to be of definite significance unless it be interpreted as indicating that the oxygen consumption diminished in response to a decrease in peripheral blood flow.

*Pulse-wave Velocity.* The results of determinations of pulse-wave velocity from the heart to subclavian artery, subclavian to brachial and femoral arteries and femoral to dorsalis pedis arteries will be found in the table. The values estimated were at no time outside the normal range. The effect of compression of the fistula was to increase the pulse-wave velocity in the arch of the aorta and peripheral vessels and to slow it in the aortic trunk. After operative closure of the fistula the pulse-wave velocity was accelerated through all parts of the vascular system except the aortic arch. It has been stated that an arteriovenous fistula causes slowing of the pulse-wave velocity<sup>18</sup> but the observations in the present case indicate

that this does not necessarily apply to all parts of the arterial system since the opposite effect may occur in individual sections.

TABLE 1.—DATA ON CASE OF ARTERIOVENOUS FISTULA.

	Fistula open.	Fistula compressed.	After operation.
Pulse rate (per minute)	70-100	48-60	52-84
Arterial pressure (in mm. Hg):			
Auscultatory: Non-basal: Systolic	140-156	150-190	110-140
Diastolic	77-96	115-130	70-84
Basal: Systolic	126	127	119
Diastolic	62	81	78
Oscillometric: Basal: End systolic	129	131	123
Lateral systolic	112	122	115
End diastolic	65	86	81
Lateral diastolic	62	81	78
End to lateral systolic diff.	17	9	8
Venous pressure (corrected, in mm. blood)	75	62	55
Respiratory rate (average per minute)	18	17	16
Respiratory minute volume (in liters)	7.8	7.3	6.0
Oxygen consumption (in cc. per min.)	247.0	247.0	265.7
Basal metabolic rate	-8.1	-8.1	-0.5
Pulse-wave velocity (in meters per sec.):			
Heart to subclavian artery	3.17	3.95	2.70
Subclavian to brachial artery	5.78	5.48	7.43
Subclavian to femoral artery	4.76	4.00	5.56
Femoral to dorsalis pedis artery	8.49	9.25	10.36
Skin temperature (in ° C.):			
Average for normal leg	34.00	34.88	
Average for affected leg	34.08	34.77	
Maximum rise, normal leg		1.45	
Maximum rise, affected leg		0.85	
Cardiac output per minute:			
Acetylene		4.26	4.07
Ethyl iodid	5.48	3.80	3.85
	5.08	4.32	3.81
	4.90		
Average in liters per min.	5.15	4.13	3.91
Cardiac index	2.64	2.12	2.02
Decrease in cardiac output, per cent		-20	-24
Cardiac output per beat	68.3 (80)	73.1 (52)	68.8 (56)
(corresponding pulse rates in brackets)	66.9 (76)	78.5 (55)	68.1 (56)
	62.0 (79)		
Average in cc. per min.	65.7	75.8	68.5
Heart size, area in sq. cm. of cardiac silhouette	194		
	141	126	108
Transverse diameter in cm.	19.5		
	16.4	15.2	12.5

*Electrocardiogram.* In the presence of the open fistula the electrocardiogram showed a normal sinus rhythm with a rate of 120 per minute. The only abnormalities noted were a *Q* wave in Lead III, a flat *T* wave in Lead I, and a diphasic *T* wave in Lead IV. Digital compression of the fistula had no effect on the record other than a slowing of the rate to 80. The electrocardiogram was repeated approximately 3 weeks after operation and showed a pulse rate of 100. There was an increased amplitude of the initial ventricular complexes in all leads, the *T* wave in Lead I was still flat, the *Q*

wave in Lead III had disappeared and the *T* wave in Lead IV had become deeply negative.

It is rather surprising that so few signs of myocardial disturbance were found in a heart so severely affected. The absence of marked change in the form of the waves on occlusion of the fistula is also of interest and agrees with the reports of other observers.<sup>5,8,22</sup> The change in  $Q_3$  and  $T_4$ , however, is indicative of definite improvement in the state of the myocardium after operation.

**Discussion.** The most important effect of an arteriovenous fistula is the remarkable degree of cardiac enlargement and its consequent circulatory insufficiency. The enlargement has been attributed to hypertrophy<sup>7,10,12,14,21</sup> and dilatation<sup>14,21,20</sup> due to the increased cardiac output and blood volume. That hypertrophy was not a significant factor in the present case is indicated by the rapid reduction in size of the heart after operation. Dilatation, therefore, appears to be the chief cause of the enlargement. However, it is difficult to explain so great a degree of dilatation by an increased output of only 24%, especially since aortic insufficiency associated with a comparable leak produces mainly hypertrophy. Nor is the increased blood volume likely to be an important factor as polycythemia very seldom causes a similar degree of enlargement.

Skin temperature and plethysmographic studies have indicated that occlusion of the fistula causes an increase in the peripheral capillary circulation even though the cardiac output is simultaneously diminished. Since coronary blood flow may safely be assumed to bear a proportional relationship to the peripheral circulation, it is clear that an arteriovenous fistula must produce a disproportion between work of the heart and the blood supply to the myocardium, the former being increased while the latter is relatively diminished. Lewis and Drury have therefore, suggested that the dilatation is "due to a deficient nutrition of the heart muscle consequent on the fall of mean arterial pressure," an explanation which seems to be the most likely one.

It is unnecessary, however, to postulate a fall of mean arterial pressure as the cause of an inadequate coronary blood flow. In the present case the mean blood pressure was well within normal limits and in fact was highest during periods of activity when the greatest degree of circulatory insufficiency occurred. The coronary blood flow is inadequate only because, although possibly normal in absolute quantity, it is below normal in proportion to the work of the heart. Under the circumstances, the myocardium may assume an increasingly hypodynamic state with resultant dilatation and congestive failure.

In the light of the present treatment of cardiac failure by ablation of the thyroid, these observations are very suggestive. They illustrate the fact that in cases of relative coronary insufficiency, a reduction of the disproportion between the work of the heart and

the coronary blood flow not only benefits peripheral congestion, but improves the function of the myocardium as well. This effect was exhibited when surgical repair of the arteriovenous fistula caused the disappearance of cardiac dilatation. In cases of coronary insufficiency due to organic changes, ablation of the thyroid similarly reduces the work of the heart to meet the limitations of the coronary blood flow. The favorable effect of this procedure depends in part upon the reduction of the body requirement for a normal minute volume. It may also depend, however, on the fact that the nutrition of the heart becomes adequate with a resultant decrease in cardiac dilatation in many cases and a definite improvement in myocardial function as exhibited by an increase in exercise tolerance.<sup>4</sup>

**Summary and Conclusions.** 1. A case of traumatic femoral arteriovenous fistula is reported together with observations made with the fistula open, during external compression of the fistula and after successful surgical repair. Significant changes in the cardiovascular system are described.

2. The inconstant relationship between the characteristic rise of blood pressure and slowing of the pulse rate on occlusion of the fistula leads to the conclusion that the bradycardiac reaction is not due exclusively to blood pressure changes.

3. The basal minute volume of the heart was increased 24% by the fistula but even in the presence of the increased output there was evidence of a relatively diminished capillary blood flow.

4. In the standing posture compression of the fistula caused a conspicuous increase in translucency of the lung fields as seen fluoroscopically, indicating a marked decrease in the blood content of the lungs.

5. The area of the silhouette and the transverse diameter of the heart were reduced by 45% following treatment. It is concluded that the cardiac enlargement was due, as Lewis and Drury suggest, to a relatively inadequate coronary blood flow.

6. It is suggested that total ablation of the thyroid in cases of coronary insufficiency may be of direct benefit to cardiac function in a manner analogous to the effect of closure of an arteriovenous fistula.

Appreciation is expressed to Dr. R. G. Torrey for much helpful criticism, to Drs. I. Starr, J. Donal and J. Scott for the measurement of the cardiac output and to Dr. B. McGlone for the estimation of the skin temperature.

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## STUDIES ON THE STRUCTURE AND FUNCTION OF BONE MARROW.

### IV. BONE MARROW IN AGRANULOCYTOSIS.

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CHANGES\* in the blood-forming organs as described in the numerous case reports of agranulocytosis have been inconsistent to a remarkable degree. On the contrary the bone marrow of 11 cases studied during the past 4 years, carefully selected as regards the clinical aspect, presented fairly constant histopathological appearances, evidenced by the fact that twice I was able to suggest the diagnosis from examination of marrow sections alone. Certain characteristic findings were barely mentioned in another article<sup>3</sup> and in a personal communication quoted by Strumia.<sup>4</sup>

In each of the first 3 articles of this series<sup>1,2,3</sup> I pointed out the need for meticulous care in the examination of the bone marrow, necessitated by its wide distribution and by the variability of the tissue in different bones at different ages. It was made clear: (1) That an examination based on marrow removed from but one locus

\* The reader is referred to the recent article of Jackson and Parker (*New England J. Med.*, **212**, 137, 1935), an able and probably the best survey of agranulocytosis.



was woefully inadequate; (2) that the tibial and femoral shafts could be regarded as representative of long bones with marrow normally fatty in the adult, the vertebrae, sternum and ribs of cancellous bone marrow normally cellular; (3) that, in any case, at least the femur and tibia as well as sternum (or vertebra) must be examined; (4) that the technique employed in the cutting and staining of sections must be of such quality that accurate cell identification is possible; (5) that smears *alone* are nearly valueless, in that the relative proportion of cells and their relationship one to another cannot be determined. Discrepancies in pathologic examinations have served to cloud the issue regarding the true nature of the disease process.

I cannot help remarking, however, that blame for much of the confusion concerning agranulocytosis rests with the clinician and the "blood stream hematologist" who have grasped at the findings of mucosal ulceration and profound neutropenia as the basis for diagnosis in so many of the reported cases. Would these same authors group together all instances of suppuration and leukocytosis? Their diagnoses can often be negated by a glance over clinical records. The more careful observers do not admit severe anemia, thrombocytopenia, hemorrhagic phenomena, splenomegaly, lymph-node enlargement and positive blood cultures of pathogens into the symptom complex of this disease; again, the history of administration of arsenicals, of exposure to benzol compounds, radium and Roentgen ray definitely catalogues various cases as secondary agranulocytosis. This would indicate that cases of aleukemic leukoses, aplastic anemia, known toxic and infectious suppression of the bone marrow have been indiscriminately classed with the idiopathic condition under discussion, *i. e.*, the *disease* agranulocytosis.

Concerning the relation of amidopyrin certain reports have indicated a positive etiologic status. A negative statement may be of some value. In the Philadelphia General Hospital (a year's admissions, 29,488; deaths, 4027) the approximate consumption of amidopyrin in 1934 was 120,000 tablets, yet not a single case of true agranulocytosis appeared in the 1926 necropsies performed during the year (neither were there instances on the clinical services with recovery). The few diagnoses of agranulocytosis that have been made in the hospital were proven by sternal biopsy or necropsy to be aleukemic myelosis (1 case), aleukemic lymphadenosis (1 case), aleukemic reticulosis (1 case), aplastic anemia (2 cases) and arsphenamin neutropenia (1 case, history obtained after biopsy ruled out agranulocytosis).

The 11 cases upon which the following bone marrow description is based conformed satisfactorily to the accepted hematologic and clinical pictures; they presented either acute progressive or chronic continuous profound neutropenia, relative lymphocytosis (actual lymphopenia), no anemia or thrombocytopenia of consequence, no

hemorrhagic phenomena; necrotizing mucosal lesions were more or less prominent and 1 case gave a history of remission and relapse. Possibilities of aleukemic leukoses, aplastic anemia, leukotoxins (other than amidopyrin and allied drugs in some instances), septic and irradiation neutropenia were completely excluded. The duration of illness varied from 3 days to more than 10 months. Sufficient similarity in the essential histopathologic changes exists to allow individual protocols to be omitted in favor of a general survey.

TABLE 1.—SUMMARY OF CLINICAL DATA.

Case No.	Aut. No.	Age.	Sex.	Duration of disease.	Type.	Leukocytes, range, thousands.	Neutrophils, range %.	Erythrocytes, range, millions.
1	UH-27-14	48	F	1 wk.	Acute	0.6-0.5	0-0	4.4-4.4
2	UH-30-18	31	F	10 dys.	Acute	1.0-0.8	0-0	4.8-4.6
3	UH-31-22	56	M	1 wk.	Acute	1.2-0.5	0-0	4.4-3.3
4	UH-31-191	23	F	{ 9 mos. 3 dys.	{ Chr. remit. Ac. termin.	3.0-1.9	7-0	4.8-4.8
5	UH-31-498	78	M	3 wks.	Acute	2.1-1.5	16-0	3.9-3.1
6	UH-31-513	58	F	1 wk.	Acute*	1.0-0.2	0-0	4.8-4.3
7	UH-31-886	52	M	3 dys.	Acute	5.0-5.0	0-0	3.6-3.5
8	UH-31-943	64	M	10 mos.	Chr. contin.	3.2-1.9	16-0	4.5-2.6
9	UH-32-138	19	M	4½ mos.	Chr. contin.	16.3-1.5	33-0	4.6-2.4
10	PH-32-62	50	F	10 mos.+	Chr. contin.	2.6-0.66	6-0	5.5-2.9
11	LH-982	?	M	6 dys.	Acute	1.7-0.5	10-2	3.7-3.2

\* Possible previous attack.

NOTE.—Cases 1, 2, 3, 5, 6, 7, 8 and 9 were used in a previous paper by Fitz-Hugh and Comroe (AM. J. MED. SCI., 185, 552, 1933), the pathologic material utilized here through their courtesy. I am indebted to Drs. Klein and Fowler of the Presbyterian Hospital for Case 10, and to Dr. Brown of the Lankenau Hospital for Case 11.

Gross description hardly justifies the effort. Soft to semifluid marrow, seemingly degenerated, may show nice preservation of cell structure; red marrow in the femur may be simple congested fat; yellow-gray marrow may be largely cellular; firm red marrow may be badly degenerated. Attention then is given here only to the microscopic picture.

Degree of cellularity varies considerably in different bones of individual cases but the qualitative changes are similar. The femur is found to be a good barometer of marrow activity, hyperplasia being roughly in direct proportion to the duration of illness; two exceptions are noted later. The earliest changes are found in the femur of Case 4 (Plate I), an instance of recurrent agranulocytosis with a terminal relapse of but 3 days' duration. The most marked hyperplasia exists in Case 10, the patient having been constantly neutropenic (600 to 2600) for over 10 months (Plate II, upper and middle). The differential cell count (1000 cells each) in these two marrows compared with the normal and two types of secondary

agranulocytosis affords an interesting basis for description and discussion.

TABLE 2.—DIFFERENTIAL MARROW COUNTS (PER CENTS).  
(*Azure II—Eosin.*) (1000 cells each.)

	Normal.*	Agranulocytosis.		Arsphen. neutropenia.	Septic neutropenia.
		Early changes (Case 4).	Marked changes (Case 10).		
Granulocyte series:					
Myeloblasts . . . . .	0.6	37.3	45.1	6.6	3.6
Promyelocytes . . . . .	9.0	2.6	9.5	8.2	6.0
Myelocytes (neutrophil) . . . . .	34.6	0.2	1.2	29.2	18.8
Myelocytes (eosinophil) . . . . .	2.0	0.1	2.5	2.2	1.2
Myelocytes (basophil) . . . . .	0.0	0.0	0.4	0.0	0.0
Metamyelocytes† (neutrophil) . . . . .	14.6	0.0	0.6	16.2	15.6
Segmented forms (all types) . . . . .	3.0†	0.0	0.0	5.0	26.2
Erythrocyte series:					
Megaloblasts . . . . .	0.0	3.5	0.5	1.0	0.2
Erythroblasts . . . . .	14.8	19.2	6.5	14.4	9.2
Normoblasts . . . . .	18.2	19.9	10.4	10.8	10.4
Thrombocyte series:					
Megakaryoblasts . . . . .	0.2	1.2	1.4	1.2	0.2
Megakaryocytes . . . . .	0.8	1.4	2.1	1.2	0.6
Reticulo-endothelial apparatus:					
Reticular forms . . . . .	2.0	7.9	3.4	3.8	3.2
Wandering forms . . . . .	0.2	1.2	1.3	0.0	3.8
Lymphatic series:					
Lymphocytes . . . . .	0.0	4.2	11.6	0.2	0.8
Plasmacytes . . . . .	0.0	1.3	3.5	0.0	0.2

(Dense folliculoid accumulations of lymphocytes were avoided in agranulocytosis cases.)

\* Case of brain tumor (white female, aged 22) with normal leukocyte count.

† Metamyelocytes include all cells between myelocyte and segmented form for simplification.

‡ This figure is lower than usual.

In early hyperplasia of fatty marrow, cells of the general reticulum tend to assume certain morphologic characters of the myeloblasts while still retaining cytoplasmic processes in relation to reticular fibrillae. Marked proliferative activity of myeloblasts is usually prominent, evidenced by the frequent appearance of mitotic figures, occasionally to a degree suggestive of myelosis; unlike myelosis, however, it does not proceed at the expense of the other marrow elements and never results in the so-called "replacement anemia" (profound, progressive anemia and thrombocytopenia). Most myeloblasts appear normal in all respects; some, however, show vacuolated cytoplasm, frayed cell margin and a nucleus sometimes shrunken and pyknotic, sometimes faded to the extent that a thin rim of chromatin marks the line of the perinuclear membrane. Acquisition of granules is preceded by the appearance of a lighter blue zone near the nucleus, usually eccentric; granules of the pro-

myelocyte are usually sparser than one finds in the normally developing cell and are occasionally polychromatic. The apparently fully granulated myelocyte may be entirely normal but one often finds the granules loosely arranged and the cytoplasmic edge ragged. The latter changes are seen in the metamyelocyte as well; these cells have been found occasionally quite agranular. Segmented forms are seen so rarely as to be negligible. In the normal individual the neutrophilic level of the blood is maintained by a marrow containing but few myeloblasts, proliferation of promyelocytes and myelocytes at an unhurried rate being quite adequate. In agranulocytosis we have a superabundance of the early progenitors of the neutrophilic leukocyte and an extreme paucity of more mature forms.

Eosinophils usually appear structurally normal, sometimes with swollen granules and are encountered nearly always in the promyelocyte or myelocyte stage; percentage varies in the individual case but seems to bear no relation to the duration of the disease. Basophils have been seen in a few instances and are regarded as of no significance.

Erythropoiesis is in all instances of the normoblastic type, the occasional appearance of megaloblasts apparently indicating hyperactivity of moderate degree, and they are noted mostly in early hyperplasia of fatty marrow. In such instances the hemopoietic capillaries described by Doan in the rabbit and Peabody in man are demonstrable. Cell morphology in this series shows no change, except for a few binuclear erythroblasts in foci of active proliferation.

The usual degenerative-regenerative balance of megakaryocytes that one finds in the normal marrow is maintained here, augmented by a greater percentage of megakaryoblasts. The marked degeneration in this cell type described by some authors has not been observed in my series.

In addition to the scattering of lymphocytes and plasmocytes throughout the marrow dense focal accumulations occur, sometimes with a loose center and closely packed rim, so that, when viewed with the low-power objective, they may appear as typical follicles. Close examination of the central portions of such lymphoid masses, however, reveals considerable numbers of large faded cells in the background; I have wondered whether they are truly lymph follicles or merely folliculoid accumulations in response to focal degeneration. They have been observed more or less distinctly in 9 of the 11 cases; such aggregations are exceedingly infrequent findings in a given series of marrows from other types of disease. Plasmocytes are often large and multinucleated, and a few Russell body cells are encountered.

The exceptional Cases 6 and 11, ill 6 and 7 days, respectively, showed a relatively hypoplastic marrow, although general qualitative changes were those already mentioned; the femur in Case 11

was entirely fatty. Cellular degeneration exceeded that of the other cases of the series (Plate III, lower), amounting in some areas to actual necrosis, with disintegrating cells lying in the background of fibrin and edematous fluid; even here the granulocyte group suffered more damage than the other cell elements.

To summarize the marrow picture, one's attention is drawn to the progenitors of the neutrophil which are conspicuous both in number and especially through the absence of granulated forms, myeloblasts representing nearly the entire group. In the early hyperplasia of the long bones the proportion of these cells to the erythrocyte series is considerably less than that in normal marrow, the two lines of cells starting from scratch, as it were. In chronic cases, however, the myeloblasts surge far ahead while erythroblastic proliferation pursues a comparatively even course or perhaps even regresses somewhat. Activity of the cells of the general reticulum is more apparent early, as well.

#### LEGENDS FOR PLATES I, II AND III.

##### KEY

ADV —adventitial cell (Marchand)	MBL —myeloblast
BT —bone trabecula	MGBL—megaloblast
END —endothelial cell	MKBL—megakaryoblast
ERBL—erythroblast	MKC —megakaryocyte
ERC —erythrocyte	MLC —myelocyte
F —fibrin	NBL —normoblast
FC —fat cell	PL —plasmocyte
L —lymphocyte	

All sections stained by modification of Maximow's azure II eosin; tissue shown in Plate I, Plate II (lower) and Plate III (upper) sectioned in celloidin, others in paraffin; photomicrographs with Leitz apochromatic optical system (red filter with Wratten and Wainwright M plates).

**PLATE I.—Upper.** Early hyperplasia of myeloblasts and erythroblasts at mid-femur with focal accumulation of lymphocytes (L) ( $\times 70$ ) (Case 4).

*Middle.* Same; proliferation of myeloblasts in marrow interstices with admixture of a few cells of the erythropoietic series ( $\times 690$ ).

*Lower.* Same; focus of normal erythropoiesis accompanied by new formation of megakaryocytes ( $\times 690$ ).

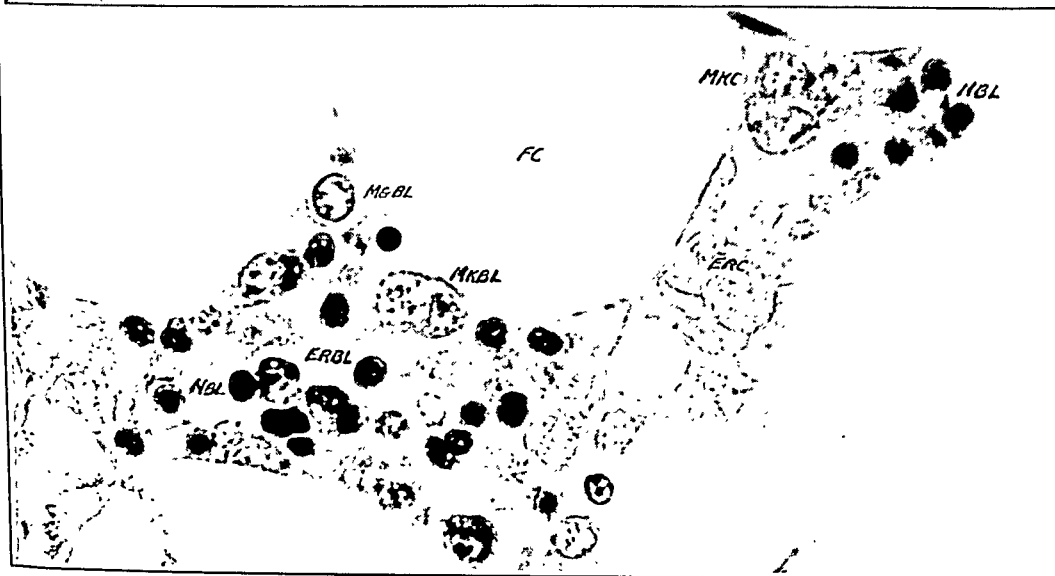
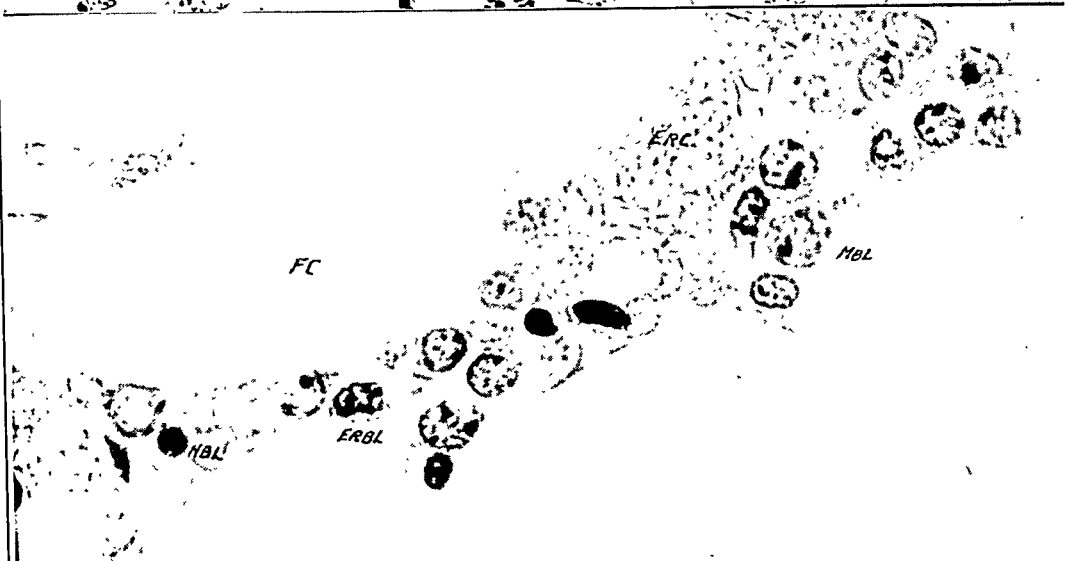
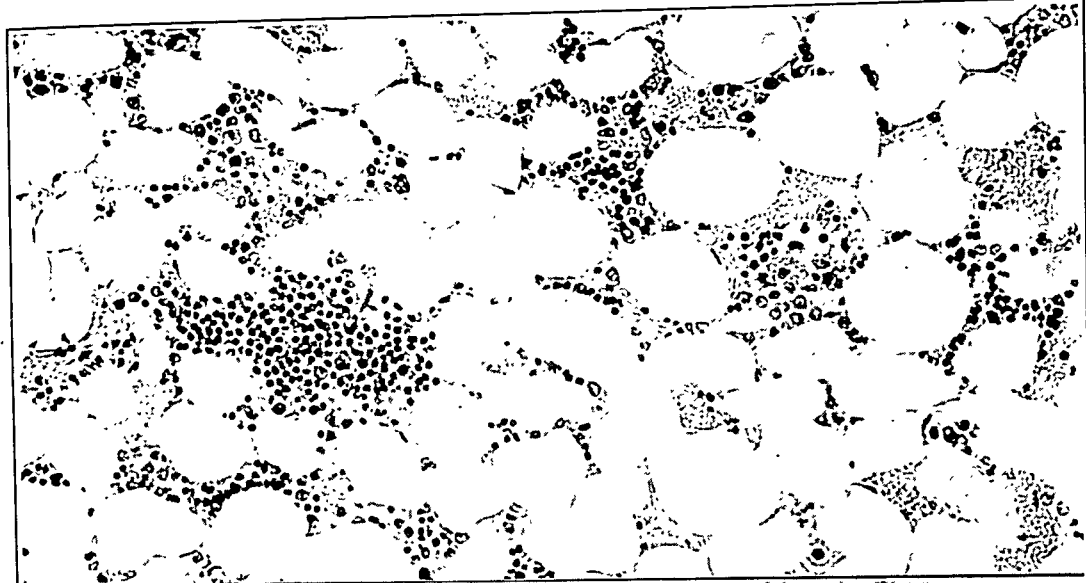
**PLATE II.—Upper.** Marked hyperplasia at midfemur, the predominant cells being the pale-staining myeloblasts; the center (L) is a folliculoid accumulation of lymphocytes; the strands of dark cells in the periphery are clumps of late erythroblasts and normoblasts ( $\times 40$ ) (Case 10).

*Middle.* High power of above shows the majority of cells to be myeloblasts, a single myelocyte, a few lymphocytes and normoblasts and a plasmocyte being admixed ( $\times 690$ ).

*Lower.* Myeloblastic proliferation in vertebra, none being differentiated beyond promyelocyte stage; a focus of normal erythropoiesis is seen in the lower left ( $\times 550$ ) (Case 2).

**PLATE III.—Upper.** Area of focal necrosis in vertebral marrow with pseudofollicular aggregation of lymphocytes; cells in the periphery are largely myeloblasts ( $\times 70$ ) (Case 2).

*Lower.* Late degeneration of myeloblasts in a background of fibrin and cell debris (vertebra); the intermingled normoblasts do not share the degeneration ( $\times 690$ ) (Case 11).



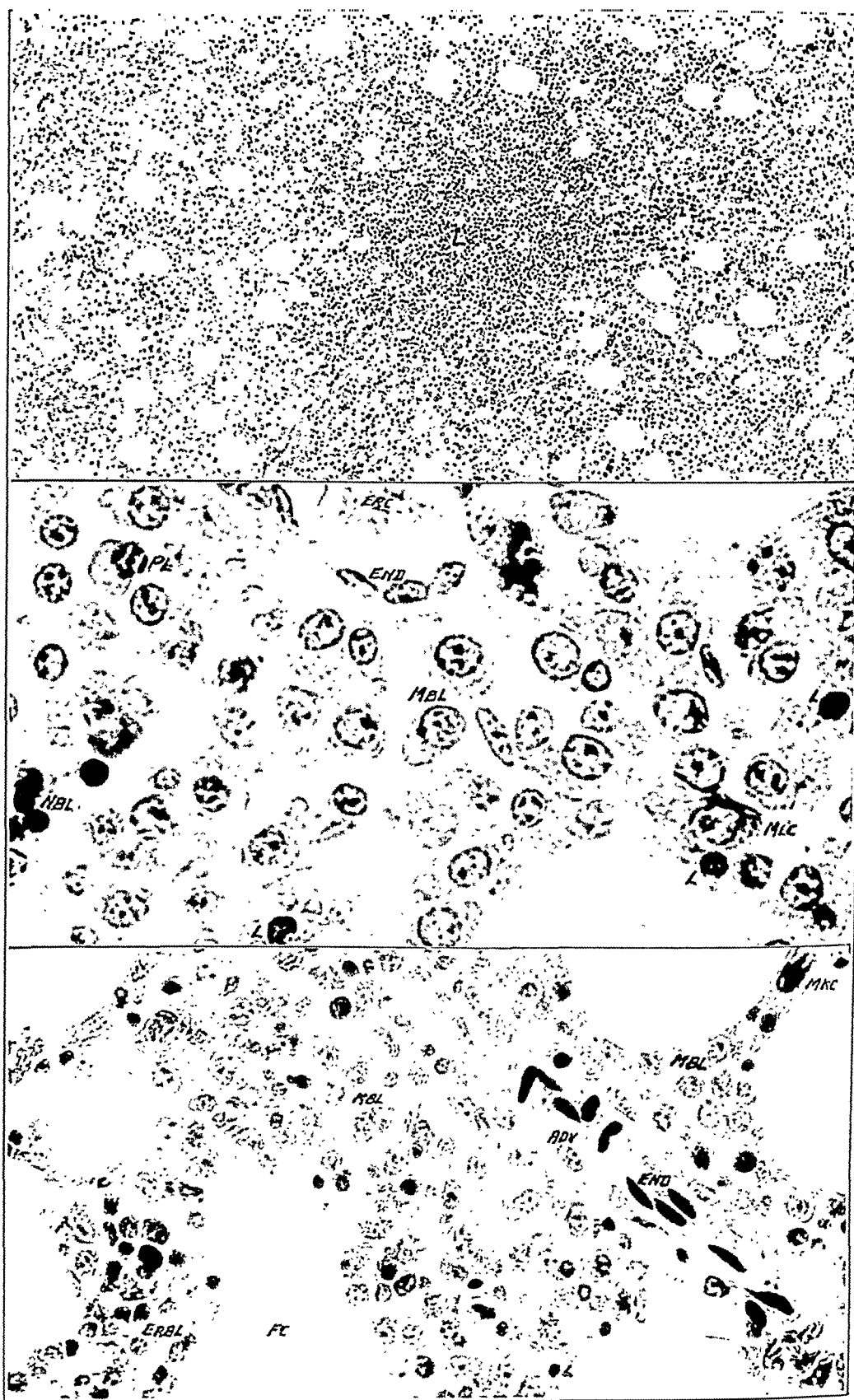


PLATE II.

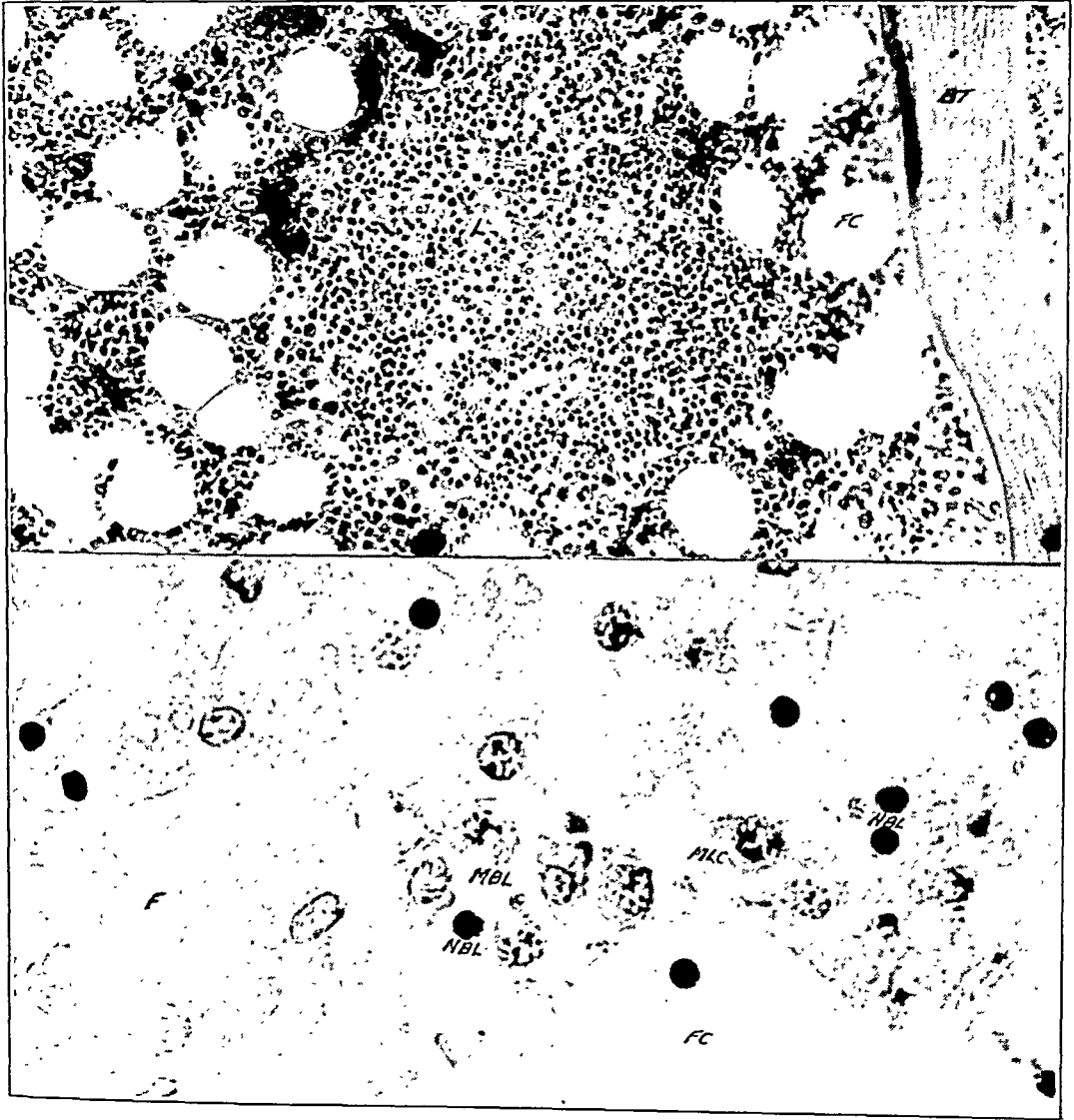


PLATE III.





Appearance of megakaryoblasts and megakaryocytes in increasing numbers with chronicity of the disease appears to keep pace with the myeloblastic hyperplasia. An infiltration of lymphocytes and plasmocytes is apparent from the first and becomes more and more prominent.

**Discussion.** My findings in the bone marrow are very similar to those carefully described by Jaffé<sup>5</sup> and include features mentioned by other observers, especially Oppikofer;<sup>6</sup> my interpretations are considerably different. The paramount feature is the failure of the actively proliferating myeloblasts to ripen into the segmented form of the neutrophil. Is this due to lack of an intrinsic maturation factor, as suggested heretofore by Fitz-Hugh and Krumbhaar,<sup>7</sup> and comparable to that of the erythron in pernicious anemia; or is it due to the influence of an extrinsic chemical or bacterial toxin? I believe the former to be true. I cannot agree with Jaffé that the marrow in arsenical and septic neutropenia does not differ from that in idiopathic agranulocytosis. The separation is difficult when one finds a relatively hypoplastic marrow, although still possible; comparison of the differential count from a typical regenerating marrow of each (Table 2) brings out a marked difference. Granular forms in the neutrophil series predominate in the arsenical and septic types and there is complete maturation never seen in idiopathic agranulocytosis; degenerative changes in the first two, when present, may affect all cell types, especially in the septic cases.

In agranulocytosis unquestionable degenerative changes in the cells of the granular series impressed me much more strongly while studying the first few cases of the series than they do now. In two of the group they are in the majority, in the others structurally good myeloid cells predominate. The first thought naturally is of a severe toxic degeneration which retards or inhibits maturation of the cells. But why specifically the granulocyte progenitors? It is obvious that myeloblasts cannot proliferate actively for days and months without some sort of disposal of their offspring; otherwise erythrocyte and thrombocyte groups would be crowded out as in the leukoses. It seems more logical to regard the degenerating forms as effete cells which succumb before reaching adolescence.

Causes of neutropenia have been schematically presented in the past. The following table, however, links the alteration in the blood with changes in the marrow in rough but practical fashion and affords the clinician better opportunity for classification of his cases as idiopathic or symptomatic agranulocytosis.

The term agranulocytosis has achieved such popularity that it will no doubt continually be applied to cases of marked neutropenia of obscure nature, whether other clinical features meet the diagnostic criteria of the idiopathic type described here or not. Fortunately, there is an increasing tendency to catalogue the atypical

cases as "secondary agranulocytosis" until the course of the disease or the pathologic findings permit proper etiologic classification (*e. g.*, arspnenamin neutropenia, etc.; compare Table 3). An analogue of the present situation may be recalled from the last century. Gretzel (1866) divorced from the leukemic leukoses, and designated as "splenic anemia" a large group of cases having common features, namely splenomegaly and anemia. Gradually the specific disease entities were withdrawn, so that, as Moynihan puts it, "the group is raided on every side. What remains? Only the forms of splenic anemia the cause of which is unknown." The raid on "agranulocytosis" is reaching such proportions that today it is the comparatively rare case that bears up under discriminating scrutiny in supporting the diagnosis of idiopathic agranulocytosis.

TABLE 3.—ABSENCE OR STRIKING DIMINUTION IN NUMBER OF NEUTROPHILS IN THE BLOOD STREAM.

- I. With relatively "full" marrow, as result of:
  - (a) Severe toxemia (usually bacterial), through primary stimulation of granulopoietic tissue, then destruction of cells *in situ* or on entry into the circulating blood.
  - (b) The leukoses (leukemias), *viz.*:
    1. Aleukemic myelosis, through overproduction of granulocytes that either do not leave the marrow or are destroyed on entering blood.
    2. Lymphadenosis, through replacement of granulopoietic tissue.
    3. Reticulosis, through replacement of granulopoietic tissue.
  - (c) Idiopathic agranulocytosis (agranulocytosis of Schultz, agranulocytic angina, malignant neutropenia), through defective maturation of myeloblasts (most cases show full marrow; see II-e).
- II. With relatively "empty" marrow, as result of:
  - (a) Severe toxemia (usually chemical), sometimes specific for neutrophils (benzol).
  - (b) Marrow exhaustion, through protracted anemia, toxemia or infection.
  - (c) Aplastic anemia (idiopathic), congenital or acquired.
  - (d) Irradiation (Roentgen ray or radium).
  - (e) Idiopathic agranulocytosis (the occasional case).

**Summary.** 1. Unwarranted diagnoses of agranulocytosis have appeared in the literature; lack of critical analysis of clinical and pathologic findings has confused the issue.

2. Meticulous study of the marrow from long and flat bones at necropsy is indicated in any case presenting marked neutropenia during life; sternal biopsy is suggested if the patient's condition permits.

3. Uniform findings in the bone marrow in 9 of 11 cases of proven idiopathic agranulocytosis are:

- (a) Marked proliferation of myeloblasts.
- (b) Failure of these cells to mature, resulting in paucity of myelocytes and practically complete absence of segmented forms.
- (c) Normal or slightly increased red blood cell formation.
- (d) Slight hyperplasia of otherwise normal megakaryocytes.
- (e) Infiltration of lymphocytes and plasmocytes.

4. Degeneration and relative hypoplasia are noted in 2 cases, although qualitative changes are similar to the other 9.

5. Comparison of differential marrow counts from idiopathic and secondary agranulocytosis (arsphenamin and septic neutropenia) shows marked dissimilarity.

6. Presence of a lesion of maturation specifically confined to the granulopoietic series, not reduplicated by diseases of known etiology, entitles idiopathic agranulocytosis, tentatively at least, to a place as a disease entity.

NOTE.—I am indebted to Dr. F. E. Ahlfeldt for assistance in a survey of the literature preliminary to this study and in collection of the material.

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## A STUDY OF THE DIAGNOSTIC VALUE OF STERNAL PUNCTURE IN CLINICAL HEMATOLOGY.

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RECENT advances in our knowledge of the disorders of the blood have made clinicians increasingly conscious of the necessity for accurate hematologic diagnosis. Formerly a routine physical examination and blood count by an intern or the hospital laboratory was considered adequate in studying cases of anemia. Today in our larger hospitals the hematologist is called in consultation as freely as the surgeon or the nose and throat specialist, and it is important that he have at his command every possible diagnostic facility.

During the past year the author has employed sternal puncture routinely on all cases of blood dyscrasias seen in consultation. Needless to say the results have been extremely interesting.

The technique of sternal puncture has been described in detail elsewhere,<sup>1</sup> so that a brief résumé only will be given. A small

area on the skin overlying the sternum opposite the 3d interspace is painted with iodine, and novocain is injected into the skin, underlying tissues and periosteum. A specially constructed needle (Fig. 1) is then driven into the spongy bone and 10 cc. of bloody fluid aspirated and mixed with 2 cc. of a 1.4% sodium oxalate solution. This mixture is centrifuged and smears are made of the buffy coat and stained with Jenner-Giemsa stain. A differential count of 1000 cells is then made.

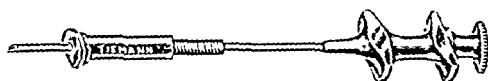


FIG. 1.—Needle used for sternal puncture

This method is practically painless and is well adapted to ward and clinic use. The small puncture heals up readily and the procedure can be repeated at frequent intervals.\*

The marrow picture not only makes the diagnosis more definite, but presents a broadening insight into the changes going on in the formative tissues. A few selected cases will aid in illustrating the value of this technique. In describing the blood and bone marrow findings the following abbreviations will be used and percentage signs will be omitted:

Neutrophil polys. (mature forms)	Polys.
Neutrophil polys. (band forms)	Polys. B.F.
Neutrophil polys. (young forms)	Polys. Y.F.
Monocytes	Mon.
Lymphocytes	Lymph.
Eosinophils	Eos.
Basophils	Bas.
Myeloblasts	MBL.
Premyelocytes and myelocytes	MCY.
Normoblasts	NBL.
Megaloblasts	MgBl.
Erythroblasts	EBL.
Proerythroblasts	PEBL.
Plasma cells	Pl.

**Case Abstracts.** CASE 1.—(Fig. 2.) Diagnosis: Normal; male, aged 32. Blood: Hb., 90; R.B.C., 5; W.B.C., 7300; Polys, 70; Lymph., 9; Mon.,

11.

Marrow: Polys., 25; Polys. B.F., 10; Polys. Y.F., 5; Lymph., 10; Mon., 1; Eos., 1; MBL., 2; MCY., 20; NBL., 15; EBL., 8; PEBL., 2; Pl., 1.

CASE 2.—(Fig. 3.) Diagnosis: Secondary anemia.

The patient, a white female, aged 57, had been slowly losing weight and strength during the past 6 months. Owing to gastric distress she had restricted her diet for the past year to milk and white cereals. On exam-

\* While the method of sternal puncture is undoubtedly of great value in the study of anemia, the examination of the material obtained in tissue sections rather than in smears would seem to be preferable. Imprint preparations break up fewer cells than do smears; with smears, preliminary suspension in serum has advantages.—EDITOR.

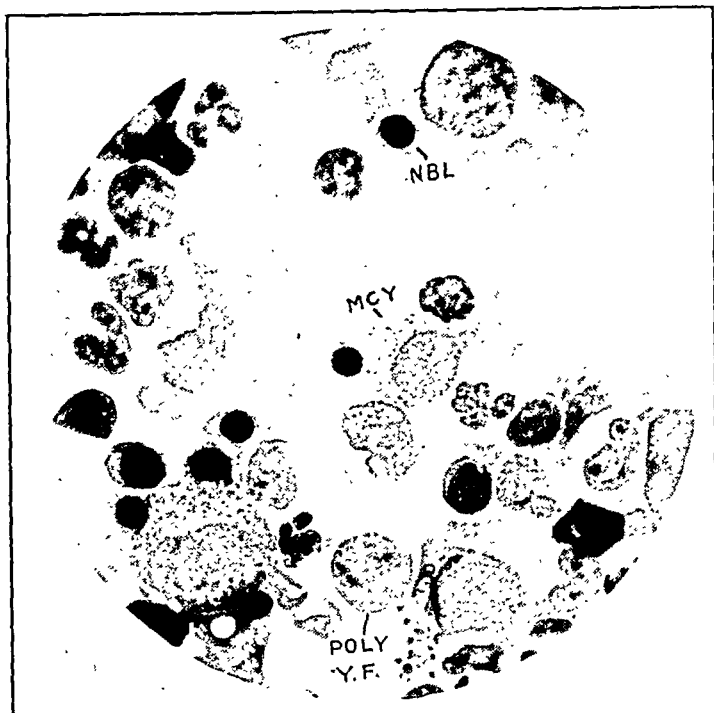


FIG. 2.—Sternal marrow. (666  $\times$ .) Normal case.

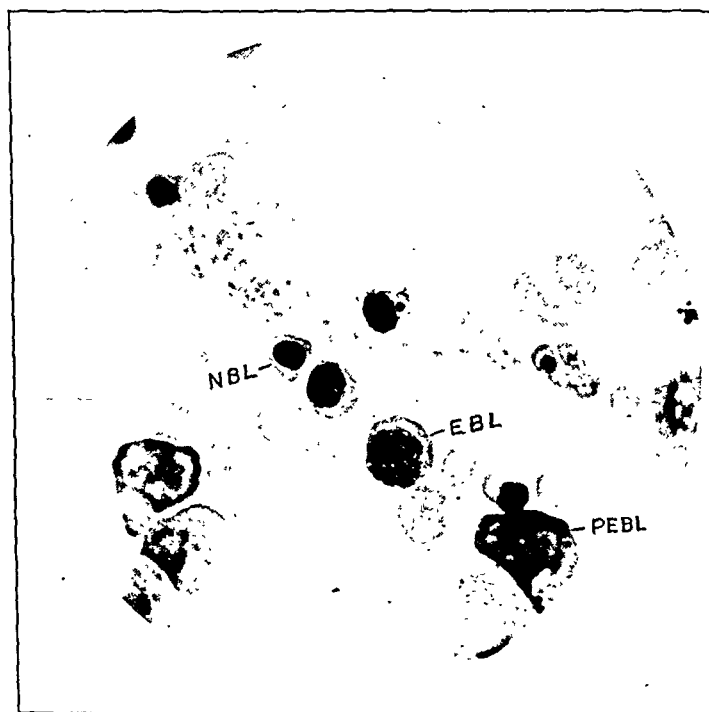


FIG. 3.—Sternal marrow. (666  $\times$ .) Case of secondary anemia. Note normoblasts (*NBL*), erythroblasts (*EBL*) and pro-erythroblasts (*PEBL*).

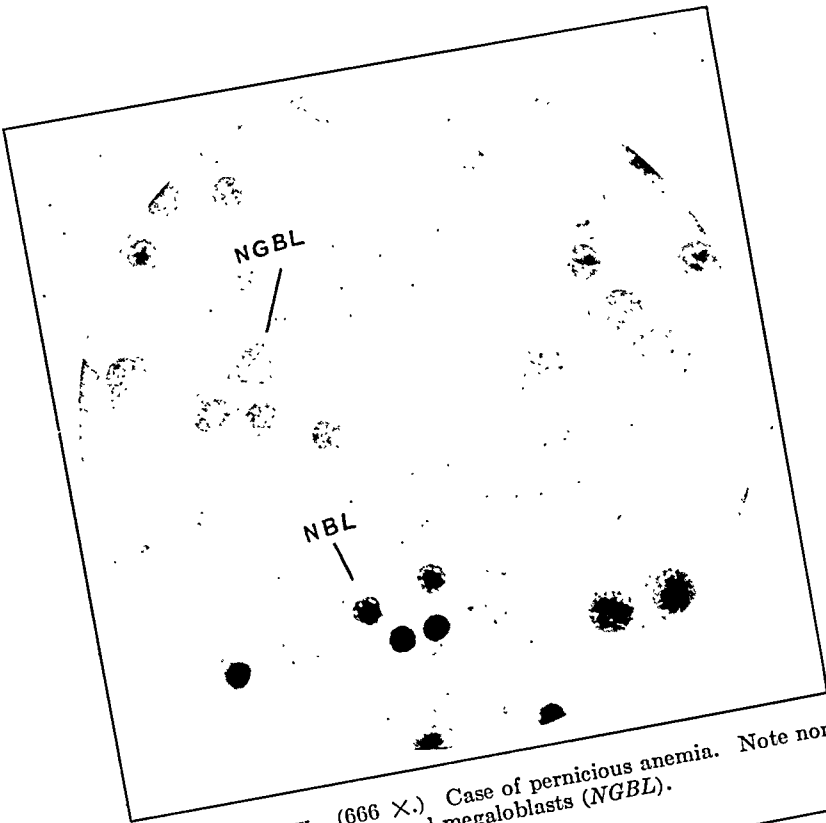


FIG. 4.—Sternal marrow. (666 X.) Case of pernicious anemia. Note normoblasts (NBL) and megaloblasts (NGBL).

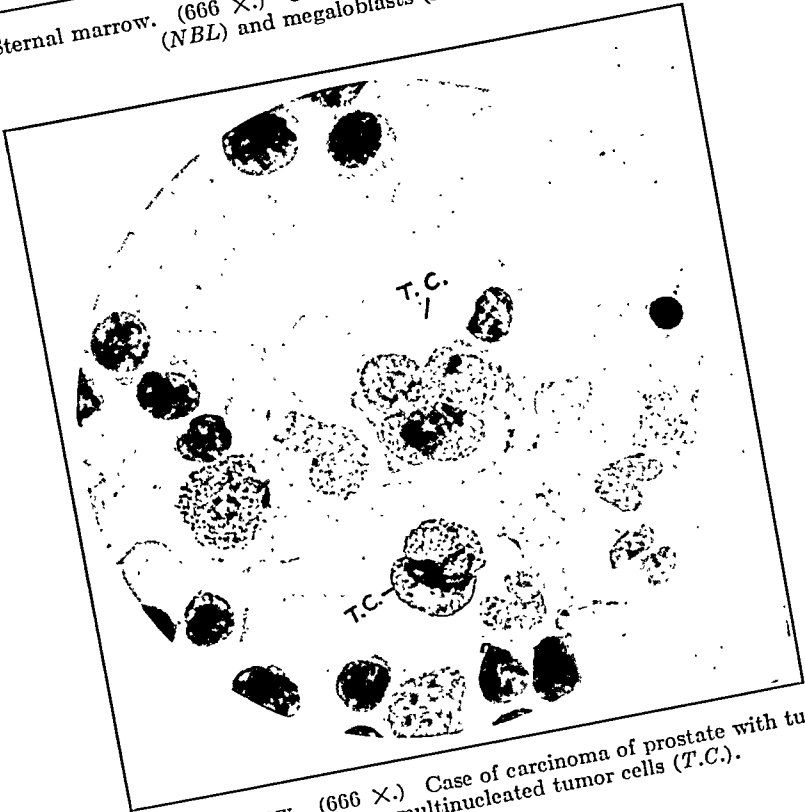


FIG. 5.—Sternal marrow. (666 X.) Case of carcinoma of prostate with tumor cells in marrow. Note multinucleated tumor cells (T.C.).

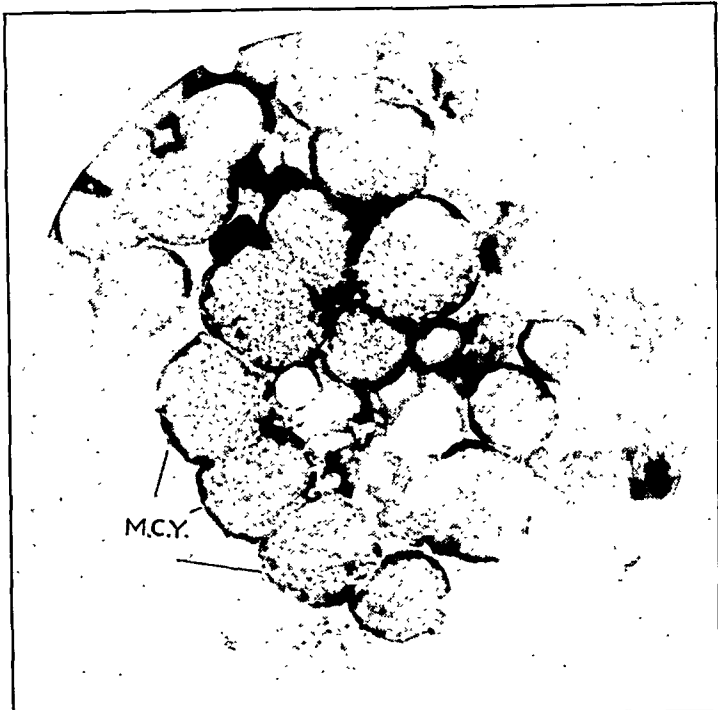


FIG. 6.—Sternal marrow. (666 X.) Case of agranulocytosis with maturation arrest. Note presence of large numbers of myelocytes (*M.C.Y.*).

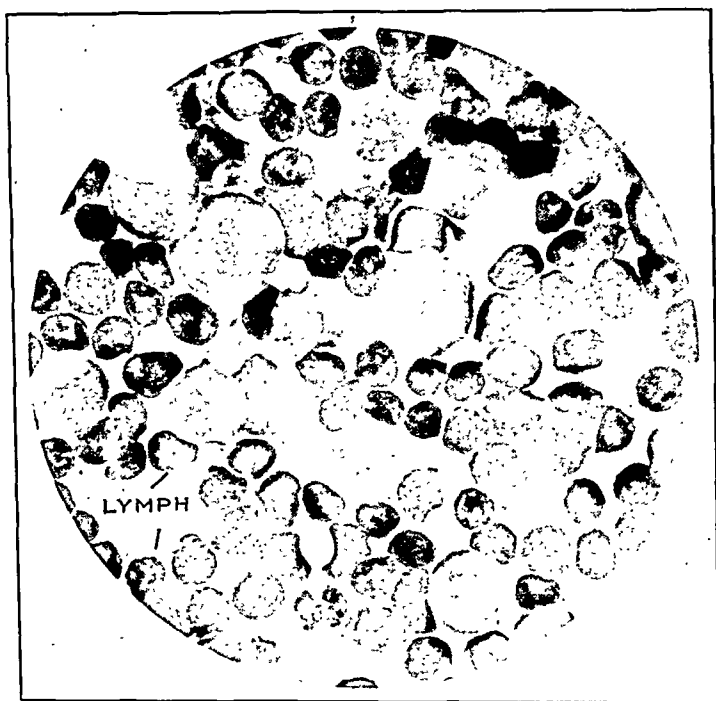


FIG. 7.—Sternal marrow. (666 X.) Case of aleukemic lymphatic leukemia. Note extensive infiltration of marrow by lymphocytes (*lymph*).



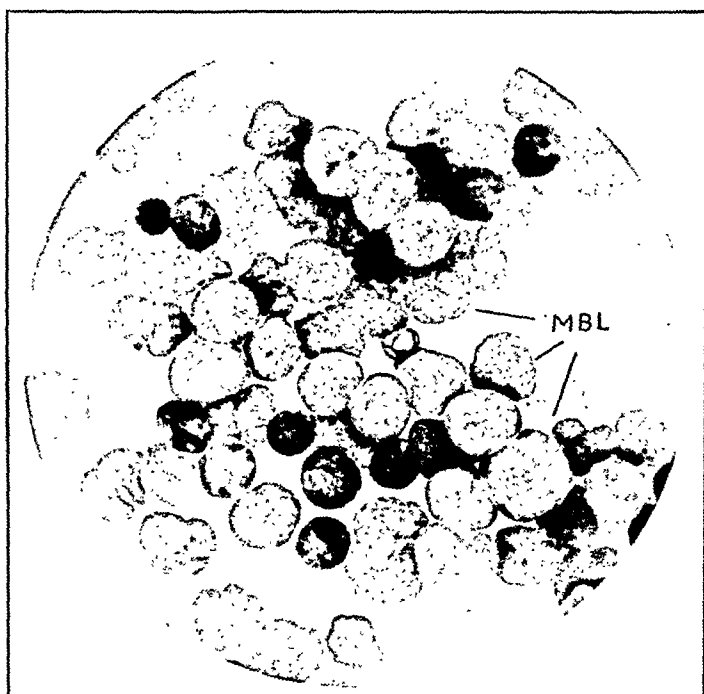


FIG. 8.—Sternal marrow (666  $\times$ .) Case of acute myeloblastic leukemia. Note tremendous proliferation of myeloblasts (*MBL*), many of which have lobulated nuclei.

ination she was quite pale and showed swollen and bleeding gums similar to those seen in scurvy.

Blood: Hb., 53; R.B.C., 2.8; W.B.C., 5000; Polys., 68; Lymph., 24; Mon., 6; Eos., 1; Bas., 1.

Marrow: Polys., 17; Polys. B.F., 13; Polys. Y.F., 5; Lymph., 5; MBL., 3; MCY., 13; NBL., 25; EBL., 15; PEBL., 3; Pl., 3.

She was put on a high-vitamin diet with particular attention to fresh fruits. Iron by mouth in large doses was also given. Recovery took place with startling rapidity.

This is a case of secondary anemia caused by dietary deficiency. It is very similar to the nutritional anemia of infancy. The bone marrow showed the typical normoblastic and erythroblastic activity seen in secondary anemia.

CASE 3.—(Fig. 4.) Diagnosis: Pernicious anemia.

The case was that of a white male, aged 46. He had a typical history of slowly increasing weakness and pallor. His tongue was atrophic and he suffered from paresthesia in the lower extremities with loss of vibratory sense over the tibia. The liver and spleen were enlarged, and the stomach contents showed no free HCl after histamin stimulation. The blood Wassermann test was negative and a gastro-intestinal barium study showed no lesions.

Blood: Hb., 68; R.B.C., 2.9; W.B.C., 5800; Polys., 58; Lymph., 24; Mon., 10; Eos., 8.

Marrow: Polys., 2; Polys. B.F., 3; Polys. Y.F., 3; Lymph., 2; MBL., 2; MCY., 3; NBL., 62; MgBl., 12; EBL., 10; PEBL., 1.

The marrow showed marked erythroblastic activity with the presence of numerous megaloblasts, which is characteristic of pernicious anemia. Treatment with liver extract produced the expected good results.

CASE 4.—Diagnosis: Carcinoma of prostate with pernicious anemia blood picture.

A man, aged 31, had increasing weakness and pallor extending over a period of several months. A diagnosis of pernicious anemia had been made elsewhere and liver treatment used to no avail. He was admitted to the hospital acutely ill, with a temperature of 105° F.

Blood: Hb., 51; R.B.C., 2; W.B.C., 1500; Polys., 20; Lymph., 70; Mon., 10.

A tentative diagnosis of agranulocytosis was made.

Marrow: Polys., 9; Polys. B.F., 1; Lymph., 3; MBL., 1; MCY., 14; NBL., 22; MgBl., 20; EBL., 26; PEBL., 3; Pl., 1.

Marked erythroblastic activity of the pernicious anemia type was seen in the marrow. The patient expired and at autopsy was found to have a carcinoma of the prostate with metastases.

This case illustrates the fact that carcinoma can often produce a blood and bone marrow picture similar to that seen in pernicious anemia.

CASE 5.—(Fig. 5.) Diagnosis: Carcinoma of the prostate. (Showing tumor cells in the marrow.)

The history of this white male, aged 60, was one of increasing weakness and ill-health. Physical examination was negative except for evidence of anemia and loss of weight. A gastro-intestinal barium study was negative as was also the blood Wassermann test.

Blood: Hb., 82; R.B.C., 4; W.B.C., 22,000; Polys., 30; Lymph., 52; Lymphoblasts, 3; Mon., 11; Eos., 3; Bas., 1.

The possibility of lymphatic leukemia was suggested.

Marrow: Polys., 22; Polys. B.F., 6; Lymph., 2; Eos., 1; MCY., 9; NBL., 4; EBL., 2; Tumor cells, 54.

Many of the tumor cells were multinucleated and did not resemble any known marrow cell.

Röntgen ray of the bones showed the mottling peculiar to carcinoma. Autopsy revealed a carcinoma of the prostate with metastases.

The presence of tumor cells in the sternum is unusual, but the sternal puncture not only ruled out leukemia in this case, but made the diagnosis of carcinoma as well.

CASE 6.—(Fig. 6.) Diagnosis: Agranulocytosis. (With maturation arrest. Recovery.)

The patient was a white female, aged 55, who had been in good health up to 1 week before admission to the hospital, when she began to get sores in the mouth and felt sick. Her temperature was 103° F. and she was quite ill.

Blood: Hb., 85; R.B.C., 4.8; W.B.C., 1100; Polys., 5; Lymph., 80; Mon., 15.

Marrow: Polys., 0; Polys. B.F., 1; Lymph., 8; MBl., 3; MCY., 70; NBl., 9; EBl., 8; PEBL., 1.

The diagnosis of agranulocytosis with maturation arrest was made and she was treated with transfusions and injections of aolan. Within a few days the temperature came down and she got well. Since that time she has been observed for a period of months and has been found to have a state of chronic agranulocytosis.

CASE 7.—Diagnosis: Agranulocytosis. (With maturation arrest. Fatal outcome.)

The case was that of a young woman, aged 20, suffering from chronic pulmonary tuberculosis. For the past few months she had taken large doses of barbiturates for insomnia. Three weeks before her demise her temperature began to mount and she had small ulcers in the mouth.

Blood: Hb., 60; R.B.C., 3.5; W.B.C., 1300; Polys., 18; Lymph., 82.

Marrow: Polys., 5; Lymph., 12; MBl., 18; MCY., 53; NBl., 10; EBl., 2.

The diagnosis of agranulocytosis with maturation arrest was made. The usual treatment was instituted, but she did not respond and expired.

CASE 8.—Diagnosis: Agranulocytosis. (With marrow aplasia. Fatal outcome.)

The patient was a white male, aged 55, who had been in the hospital for 2 months, suffering from a poorly healing fracture of the left hip. Ten days before his death he began to feel vaguely ill and his temperature rose to 103° F. The abdomen was distended and tender and at times he was irrational.

Blood: Hb., 53; R.B.C., 2.5; W.B.C., 1500; Lymph., 80; Mon., 20.

The sternal puncture yielded a markedly diminished quantity of bone marrow. The count was:

Marrow: Lymph., 70; Mon., 10; MCY., 1; EBl., 4; Pl., 9; PEBL., 6.

A diagnosis of agranulocytosis with marrow aplasia was made.

The patient did not respond to any therapy but ran a continued high temperature and died 10 days after the onset of this acute illness.

Autopsy: Bronchopneumonia, acute pericarditis, acute splenitis and marked ulcerations of the small and large intestine.

It was interesting to note that on microscopic examination no polys. could be found in the pneumonic areas in the lung.

The last 3 cases of agranulocytosis illustrate very well the underlying pathologic changes so well described by Fitz-Hugh and Krumbhaar.<sup>2</sup> A large number of these cases show a hyperplasia of the myeloid elements rather than an aplasia, and strengthens the suggestion that in many instances the condition is secondary to a maturation arrest.

CASE 9.—(Fig. 7.) Diagnosis: Aleukemic lymphatic leukemia.

The patient was a white male, aged 55. He had large masses of glands in the neck, axilla and groin, along with enlargement of the spleen.

Blood: Hb., 80; R.B.C., 4.1; W.B.C., 6000; Polys., 53; Lymph., 32; Mon., 10; Eos., 5.

Marrow: Polys., 3; Polys. B.F., 3; MCY., 4; NBl., 3; Lymph., 87.

The marrow showed a marked infiltration with lymphocytes and a diagnosis of aleukemic lymphatic leukemia was made. Biopsy of a lymph node confirmed this diagnosis.

CASE 10.—Diagnosis: Lymphoma.

For the past few years, the patient, a male, aged 70, had noticed swelling of the glands in his neck, axilla and groin. These glands were markedly enlarged, as were also the spleen and liver. He came into the hospital suffering from dyspnea and was found to have a left hydrothorax. The temperature was normal. Chest tap yielded 1500 cc. of chylous fluid, with improvement in his symptoms.

Blood: Hb., 105; R.B.C., 5.5; W.B.C., 10,200; Polys., 50; Polys. B.F. 10; Lymph., 37; Mon., 1; Eos., 2.

There was some talk of lymphatic leukemia, but the lack of anemia seemed to be against this.

Marrow: Polys., 52; Polys. B.F., 12; Polys. Y.F., 3; Lymph., 16; Bas., 1; Eos., 10; MCY., 5; NBl., 1.

The lack of lymphocytic infiltration in the marrow was definitely against leukemia. *Biopsy* of a lymph node was diagnosed as lymphoma, with no evidence of leukemia.

CASE 11.—(Fig. 8.) Diagnosis: Acute myeloblastic leukemia.

The case was that of a male, aged 23. He had always been well up to 1 month before admission to the hospital. At this time he began to complain of weakness and shortness of breath. On admission to the hospital he was acutely ill. His temperature was 102° F., the spleen was slightly enlarged and there were hemorrhages in the eyegrounds.

Blood: Hb., 35; R.B.C., 2.2; W.B.C., 150,000; Polys., 5; Lymph., 11; MCY., 3; MBl., 81.

There was some doubt in the mind of one of the clinicians as to whether these cells were myeloblasts or lymphoblasts.

Marrow: MBl., 92; NBl., 8.

The diagnosis of acute myeloblastic leukemia was, therefore, definitely established.

**Summary.** From a study of the cases cited, it is seen how valuable sternal puncture may be in differentiating the various types of anemia, in establishing the diagnosis of leukemia in doubtful cases and in differentiating aleukemic lymphatic leukemia from agranulocytosis. In 1 instance it was even possible to see tumor cells in the sternal marrow, although this is very unusual.

This method of investigation does much more for the hematologist, however, than aid him in his diagnosis. It gives him an insight into the fundamental processes underlying his findings in the peripheral blood and opens new avenues of clinical research. It is now possible to study the changes in the bone marrow almost as frequently as those in the peripheral blood and to observe the direct effect of therapy on the formative tissue.

**Conclusions.** 1. A technique of sternal puncture was described which can be done repeatedly with a minimum of discomfort to the patient.

2. A series of cases were reported which show that study of the bone marrow obtained in this way is of great assistance in hematologic diagnosis.

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### THE EFFECT OF ULTRAVIOLET RAYS ON SNAKE VENOMS.\*

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IN recent years the subject of snake venoms has been of interest not only from the standpoint of toxicology but also to some extent from that of experimental therapeutics. As far back as 1910 and 1914, papers were published by Mays,<sup>1</sup> Fackenheim,<sup>2</sup> Prévost,<sup>3</sup> Jenkins and Pendleton,<sup>4</sup> Thom<sup>5</sup> and others on the uses of crotalin, or the poison of rattlesnake, in the treatment of epilepsy; and within the last year or two, French investigators have reported studies concerning the use of cobra venom in the treatment of inoperable malignant tumors.<sup>6,7,8,9,10</sup> The present investigation was undertaken for the purpose of advancing our knowledge concerning the various factors and conditions influencing the activity of snake venoms and concerning methods of standardizing and preserving them for experimental work.

It is common knowledge that many drugs and chemicals are affected by physical agents, particularly by heat and light. It is also well known that suspensions or solutions of snake venoms decompose on standing and deteriorate under the influence of temperature. The venoms of the *Crotalidæ* are especially labile and easily affected in this respect. The venoms of the *Elapidæ*, and particularly that of *Naia* or cobra, are more resistant to heat. With regard to the effect of light on snake venoms, Calmette<sup>11</sup> noted that solutions of these toxins deteriorate when exposed to sunlight. Noguchi<sup>12</sup> studied the photodynamic effect of eosin and erythrosin on snake venoms and found that in sunlight these dyes decrease the toxicity of the venoms. Massol<sup>13</sup> found that the rays of the quartz lamp decomposed cobra venom; and Phisalix<sup>14</sup> noted

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that very long exposure (for 60 hours) of this toxin to radium radiations reduced its activity. The present investigation is devoted to a more detailed study of different ultraviolet radiations on a number of snake venoms.

**Method.** Studies were made chiefly on the venoms of two great classes of snakes, namely, of the Elapidæ, the principal representative of which is the cobra; and on the poisons of the viper group, the Crotalidæ, the American representative of which is the rattlesnake. In all experiments performed, the dried scales of venom were dissolved or brought into a colloidal solution either in water or, more often, in physiologic saline. The cobra venom employed in this investigation was obtained through the courtesy of Prof. R. N. Chopra, of the School of Tropical Medicine, Calcutta, while the Crotalus venom, or the poison of the rattlesnake, was procured through the kindness of the Mulford Biological Laboratories, Philadelphia. Venom was obtained from different species of rattlesnake, namely, the Crotalus atrox, Crotalus ruber and Crotalus exsul. In addition, other experiments were made with the venoms of Ancistrodon, or copperhead, and Bothrops atrox, South American viper.

In accordance with the character of experiment to be performed, the dried scales of venom were rubbed up carefully in glass mortars with either distilled water or saline solution. As will be seen later, venom suspensions prepared from different samples of snake poisons varied greatly in their potency. Whenever a pharmacologic experiment was performed, therefore, great care was taken to make suitable control tests in order to establish the toxicity of the solution used on each particular day.

*Method of Irradiation.* Ultraviolet radiations were obtained from mercury vapor quartz lamps. The particular apparatuses used were the Alpine Sun lamp and the Kromayer lamp of the Hanovia Manufacturing Company. Since the Alpine Sun lamp emits and generates a great deal of heat, which must be taken into account in studying the effect of ultraviolet rays on chemicals and drugs, most of the experiments were made with the water-cooled Kromayer lamp. When this apparatus is used, temperature need not be considered. The quality and quantity of radiations emitted by the Kromayer lamp are shown in the subjoined graph, prepared by Dr. W. T. Anderson, Jr. This chart indicates the distribution of spectral energy of the burner employed in the experiments at a distance of 4 inches from the window of the Kromayer lamp. When the present investigation was in progress, the intensity of radiation was considerably greater because snake venom solutions in small quartz tubes were placed directly against the window of the Kromayer lamp. In addition to such radiations as are indicated in Fig. 1, the Alpine Sun lamp emits waves as low as 1800 Ångström units which are absorbed by the water of the Kromayer lamp, and also some longer waves.

Studies on the effect of such ultraviolet irradiation on snake venoms were made not only with the total energy emitted by the Kromayer lamp but also with longer and shorter ultraviolet rays emitted by the lamp, respectively, when various filters were used. Specifically, some experiments were made with rays passed through a Wood filter, which cuts out all but the very long ultraviolet rays, while others were performed with rays passed from a Kromayer lamp through a clear quartz cylinder containing chlorin gas, which absorbs the wave lengths between the regions of 3000 and 4050 Ångström units and allows only the shorter ultraviolet rays to be transmitted.

Through the courtesy of Dr. C. F. Burnam, of the Howard A. Kelly Hospital, Baltimore, the writer was also enabled to study the effects of hard Roentgen rays and radium radiations on snake venoms.

*Pharmacologic Methods of Study.* The toxicity or potency of the venoms was assayed or tested on mice, rats, guinea pigs, rabbits and cats. In this connection, mice were found to be the most useful and economical test objects; and nearly 300 experiments were performed on these animals, the average weight of which was about 20 gm. Injections in both mice and rats were made by the subcutaneous, intramuscular and intraperitoneal routes. No marked difference in the onset of toxic symptoms was noted after parenteral and intraperitoneal injections, respectively. In order to make a more detailed analysis of their pharmacologic action on the circula-

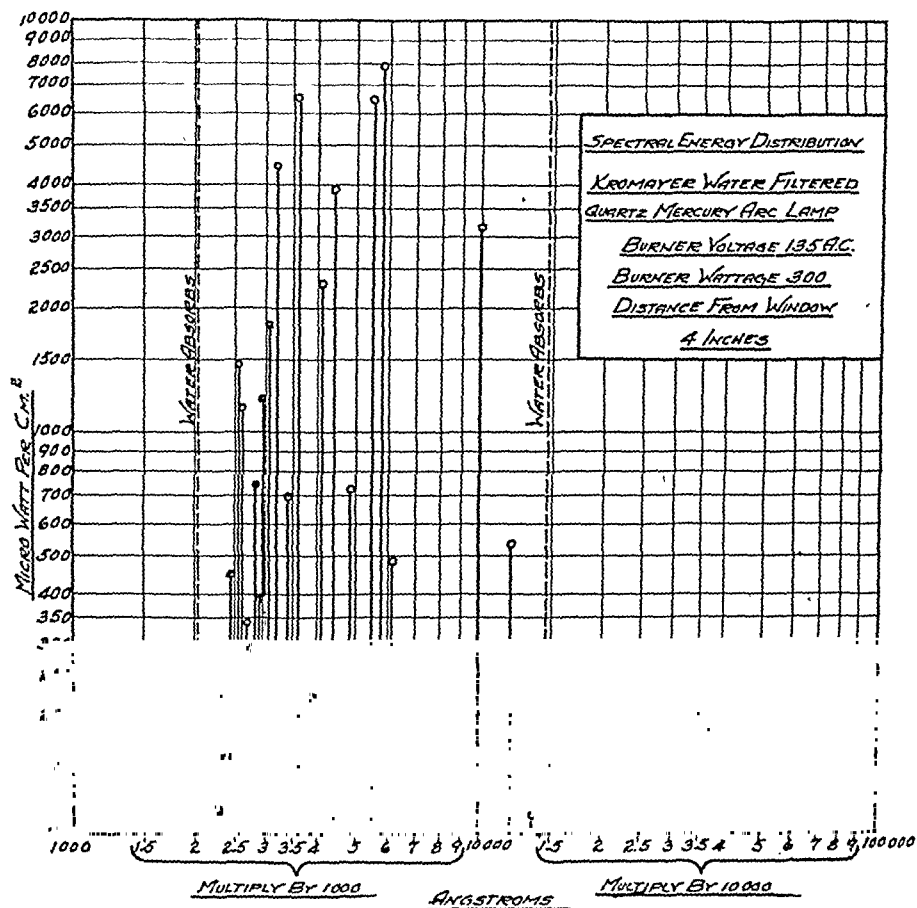


FIG. 1.—Distribution of spectral energy of burner employed in experiments.

tion and respiration, very dilute solutions of venom were injected intravenously at regular intervals in cats kept under light ether anesthesia. Such injections were made through the femoral vein while blood pressure tracings were recorded from a cannula inserted into a carotid artery; and respiratory tracings were obtained directly through the trachea by a method which the author has described elsewhere.<sup>15</sup> Beside the zoöpharmacologic studies mentioned above, parallel experiments were made on phytopharmacologic test objects, namely, on the living seedlings of *Lupinus albus*, which have been found to be susceptible to snake venom solutions.<sup>16</sup>

The entire investigation was divided into two distinct parts. One series of experiments was devoted to the study of the effects of ultraviolet radiations on various suspensions of snake venoms in quartz cells or containers. Another series of experiments was performed for the purpose of discovering the effect of ultraviolet irradiation on animals *previously* injected with varying doses of snake venoms. The object of these experiments was to ascertain whether any antidotal or antagonistic, and hence therapeutic, effect could be secured by such irradiation. A detailed description of the results obtained follows:

**Irradiation of Venom Solutions.** *Effect of Total Radiation.* Colloidal suspensions of rattlesnake and cobra venoms were made in physiologic saline, placed in rectangular quartz cells, and irradiated in the manner described above for varying periods. It was found that even a short exposure (*i. é.*, for 5 minutes) of the solutions to the rays emitted by the Kromayer lamp produced rapid deterioration of their toxicity, as indicated by biological tests on both plants and animals. In this respect it was noted that cobra venom was somewhat more resistant to ultraviolet rays than rattlesnake venom, but all the other snake venoms proved to be sensitive to the radiations of the mercury vapor lamp. Exposure for 5 minutes produced a noticeable decrease in toxicity, while a 10-minute exposure to the Kromayer lamp effected a marked deterioration of the venom solutions. The results obtained in various experiments are well illustrated by Tables 1 and 2.

TABLE 1.—EFFECT OF PROGRESSIVE IRRADIATION OF COBRA VENOM WITH KROMAYER LAMP.

<i>In Experiments on Mice.</i>	<i>In Experiments on Lupinus Albus.</i>
1. Injected 0.1 mg. of cobra venom, unirradiated. Dead in 1 hour and 35 minutes.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, unirradiated, 53%.
2. Injected 0.1 mg. of cobra venom, irradiated 10 minutes. Dead in 15 hours.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, irradiated 10 minutes, 68%.
3. Injected 0.1 mg. of cobra venom, irradiated 20 minutes. Made sick but recovered.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, irradiated 20 minutes, 79%.
4. Injected 0.1 mg. of cobra venom, irradiated 30 minutes. Very little toxicity exhibited.	Phytotoxic index of growth of seedlings in 1 to 100,000 solution of cobra venom, irradiated 30 minutes, 85%.

Table 1 shows the effect of progressive irradiation of solutions of cobra venom when quartz cells containing them were placed against the window of the Kromayer lamp. Experiments on both mice and seedlings of *Lupinus albus* revealed a striking, progressive deterioration of the cobra venom thus irradiated. Whereas the normal killing time of the solution for mice was 1 hour and 35 minutes,



the killing time of the same solutions after irradiation for 10 minutes was 15 hours. More prolonged irradiation rendered the solutions no longer fatal. Similarly the phytotoxic index of *Lupinus albus* seedlings grown in a solution of 1 to 100,000, which was originally 53%, rapidly rose to a higher figure with progressive irradiation of the venom. Table 2 shows the effect of venoms of the rattlesnake (*Crotalus exsul*), the South American viper (*Bothrops atrox*), the copperhead (*Ancistrodon piscivorus*) and of the cobra (*Naia tripudians*) on the growth of *Lupinus albus* seedlings. Phytopharmacologic tests were especially useful in comparative studies performed simultaneously on various solutions. The table shows the average root growth at a temperature of 21° C., for 24 hours, of 50 seedlings in solutions of snake venoms as compared with growth of control seedlings in normal plant-physiologic solution. The toxicity of the venoms both before irradiation and after exposure to the Kromayer lamp for 15 minutes is here recorded. In these studies the writer employed a concentration of cobra venom higher than that used in the experiments recorded in Table 1.

TABLE 2.—EFFECT OF VENOMS ON GROWTH OF LUPINUS ALBUS.

Venom.	Concentration.	Phytotoxic index of seedlings grown in.	
		Fresh emulsion, %.	Emulsion exposed to Kromayer lamp for 15 min., %.
<i>Crotalus exsul</i> . . . . .	1 to 10,000	36	77
<i>Bothrops atrox</i> . . . . .	1 to 10,000	55	100
<i>Ancistrodon piscivorus</i> . . . . .	1 to 10,000	44	100
<i>Naia tripudians</i> (cobra) . . . . .	1 to 10,000	32	88

*Effect of Long Rays.* In order to ascertain accurately the effectiveness of different ultraviolet rays in the detoxification of the venoms, experiments were made in which rays from the Kromayer lamp were passed through various filters excluding certain wave lengths and transmitting others. In this investigation, the two filters used were the Wood filter and a chlorin gas filter. The Wood filter, made of nickel oxid glass, cuts out all short waves emitted by the mercury lamp and transmits only the wave lengths over 3000 Ångström units. Solutions of venoms were exposed to rays transmitted through such a filter, and it was found that even after very long exposures (of 1 hour or more) little or no change had been produced in the potency of the venoms. The following protocol will illustrate the findings obtained in such experiments:

*Experiment of May 22, 1934.*

1. Five control mice were each injected with 0.1 mg. of cobra venom in solution, which had not been irradiated. Average killing time, 1 hour and 25 minutes.
2. Three mice were each injected with 0.1 mg. of the same solution, previously irradiated for 1 hour by rays passing through Wood filter. Average killing time, 1 hour and 30 minutes.

*Effect of Short Waves.* The effect of the short ultraviolet rays emitted by the Kromayer lamp was studied as follows: A clear quartz cylinder containing chlorin gas was interposed between the Kromayer lamp and the venom solutions. Such a filter cuts out all the ultraviolet rays ranging from 3000 to 4000 Ångström units but transmits those of shorter wave length. The following protocols indicate clearly that exposure to such short waves for 1 hour produced but little decrease in toxicity of the venoms.

*Experiment of May 23, 1934.*

(With Rays Transmitted Through a Chlorin Gas Filter.)

1. Four mice were each injected with 0.1 mg. of cobra venom solution, which had not been irradiated. Average killing time, 1 hour and 26 minutes.
2. Four mice were each injected with 0.05 mg. of cobra venom solution, which had not been irradiated. Average killing time, 6 hours.
3. Four mice were each injected with 0.1 mg. of cobra venom solution, which had been irradiated for 30 minutes. Average killing time, 1 hour and 30 minutes.
4. Two mice were each injected with 0.1 cobra venom suspension which had been irradiated for 1 hour and 15 minutes. Average killing time, 20 hours.
5. Two mice were each injected with 0.05 mg. of cobra venom, which had been irradiated for 1 hour and 15 minutes. Both recovered.

**Irradiation of Poisoned Animals.**—The destructive action of ultraviolet rays on snake venom solutions in quartz containers having been established, the next step was to inquire whether such rays are capable of destroying or at least of decreasing the virulence of the venoms after they have been injected in animals. Accordingly, experiments were made on mice to which the venoms were administered in various ways; and, after injection, the animals were exposed to the rays of either the Kromayer lamp or the Alpine Sun lamp. In some experiments, such injections were made subcutaneously; in others, intramuscularly; and in still others, intraperitoneally. The animals in small cages were exposed to the rays of the Kromayer lamp at a distance of 20 cc. from the window. When the Alpine Sun lamp was employed for irradiation, the usual distance of the cage containing the animals from the mercury arc was about 60 cm. It may be stated at once that control experiments on normal mice, which had *not* been injected with snake venom revealed that such irradiation for protracted periods of time (*i. e.*,  $\frac{1}{2}$  hour or more) had no deleterious effect on these animals.

It was surprising to discover that the findings obtained in tests on animals were not at all in agreement with those obtained in experiments in which the venom had been placed in quartz containers and exposed to ultraviolet radiations. Animals injected with snake venom and then placed under mercury vapor lamps exhibited no diminution of toxic symptoms. Instead of exerting an antagonistic or detoxifying action, the irradiation of the injected

mice produced either no difference in the killing time of the animals or, as was more often the case, somewhat accelerated the onset of death. This was particularly true of cobra venom injections. Similar observations were made with *Crotalus* venom occasionally; when injections of solutions of this venom were made in the skin of the back—that is, in a site from which the poison was not readily absorbed—a decrease in the toxicity or delay in the onset of toxic symptoms was noted. Such an effect, however, was never observed after injection of cobra venom by any route.

TABLE 3.—EFFECT OF IRRADIATION BY ALPINE SUN LAMP ON MICE AFTER INJECTION OF *CROTALUS ATRON* VENOM.

Mouse No.	Injected.	Irradiated.	Effect.
1 . .	Not injected	30 min.	None.
2 . .	0.5 mg., subcut.	Unirradiated	Dead in 1 hr., 45 min.
3 . .	0.5 mg., intraperit.	Unirradiated	Dead in 1 hr., 50 min.
4 . .	0.5 mg., intraperit.	30 min.	Dead in 1 hr., 24 min.
5 . .	0.5 mg., intramus.	30 min.	Dead in 1 hr., 35 min.
6 . .	0.5 mg., subcut.	30 min.	Dead in 1 hr., 7 min.
7 . .	0.5 mg., intraderm. in back	30 min.	Dead in 5 hr.

TABLE 4.—EFFECT OF IRRADIATION WITH KROMAYER LAMP ON MICE INJECTED WITH COBRA VENOM.

Mouse No.	Administered, % of mg.	Injected.	After injection.	Dead in.
1 . . .	0.250	Subcutaneously	Irradiated	17 min.
2 . . .	0.250	Subcutaneously	Unirradiated	16 min.
3 . . .	0.200	Intraperitoneally	Irradiated	25 min.
4 . . .	0.200	Intraperitoneally	Unirradiated	31 min.
5 . . .	0.100	Subcutaneously	Irradiated	2 hr., 12 min.
6 . . .	0.100	Subcutaneously	Unirradiated	2 hr., 37 min.
7 . . .	0.100	Intraperitoneally	Irradiated	1 hr., 38 min.
8 . . .	0.100	Intraperitoneally	Unirradiated	2 hr.
9 . . .	0.050	Intraperitoneally	Irradiated	2 hr., 19 min.
10 . . .	0.050	Intraperitoneally	Unirradiated	2 hr., 39 min.
11 . . .	0.050	Intramuscularly	Irradiated	2 hr., 19 min.
12 . . .	0.050	Intramuscularly	Unirradiated	2 hr., 39 min.
13 . . .	0.025	Subcutaneously	Irradiated	5½ hr.
14 . . .	0.025	Subcutaneously	Unirradiated	Died overnight
15 . . .	0.020	Intraperitoneally	Irradiated	Recovered.
16 . . .	0.020	Intraperitoneally	Unirradiated	Recovered.

The results obtained are well illustrated in the subjoined Tables 3 and 4. Table 3 shows the effect of irradiation with the Alpine Sun lamp on 6 mice, previously injected with rattlesnake (*Crotalus atrox*) venom. The first or control mouse, which was not injected with snake venom at all, was exposed to ultraviolet rays and exhibited no toxic symptoms. The table shows the killing time of mice injected with the venom, some of which were irradiated while others were not. No marked difference in the killing time of the two sets of mice was noted; only in case of mouse No. 7, which had been injected intradermally in the back and exposed to ultraviolet

rays was the onset of death delayed. Table 4 shows the effect produced by injections of various doses of cobra venom in pairs of mice, 1 of which was exposed to ultraviolet radiations while the other was not. Here again, it will be noted that very little detoxification resulted from exposure of injected mice to ultraviolet rays.

Since detoxification did occur occasionally when the venom solution was injected in locations from which absorption was poor, additional experiments were made with solutions of venom combined with drugs, tending to prevent absorption. Such experiments were made with small doses of epinephrin, in some animals, and of solutions of sodium sulphate in others; and it was found that neither of these promoted detoxification of the venoms by ultraviolet rays.

**Analysis of Results.** The great difference between the effects of ultraviolet rays on snake venoms in quartz cells outside the body and their action on these toxins *in vivo* calls for an explanation. Various hypotheses may be advanced. It may be assumed that after injection the venom rapidly combines with body tissues and is no longer present in a form easily disintegrated by ultraviolet rays. Such an hypothesis does not tally with the fact that the poisonous action of cobra and other snake venoms for mice is not very rapid and that the minimal lethal dose for these animals usually produces death in an hour or more. Again, it may be argued that the ultraviolet rays do not destroy the venom injected in those animals because they do not sufficiently penetrate the skin and tissues of the animals. This view is not tenable, considering the fact that ultraviolet irradiations have been proven to be of undoubted efficacy in the treatment of rickets and other clinical diseases. Moreover, Macht, Anderson and Bell have shown that the penetration of ultraviolet rays, especially those with wave lengths between 3000 and 4000 Ångström units, through living tissue is much greater than was formerly supposed.<sup>17,18</sup> A third explanation for the difference between the effects of the rays on venoms in quartz cells and their action on the same toxins *in vivo* was obtained by actual experiment.

Solutions of cobra venom were prepared and divided into two portions. One-half was placed alone in a quartz cell. To the other half of the solution a small quantity of clear blood serum was added, and the mixture was placed in another quartz cell of the same proportions. The 2 specimens were irradiated simultaneously with the same lamp for the same length of time. The toxicity of each was then tested on mice and other animals. It was found that exposure of the plain venom solution in physiologic saline to the ultraviolet rays resulted in a marked decrease in its toxicity. On the other hand, exposure to ultraviolet rays of the snake venom solution, to which 5% or more of blood serum had been added,

produced very little change in its toxicity. The results obtained are concretely illustrated by the following protocols:

*Experiment of October 9, 1934.*

*Mouse No. 1 (Control).*

10.20 A.M.: Injected with 0.5 cc. of cobra venom solution (1 mouse unit).

2.10 P.M.: Dead.

*Mouse No. 2.*

10.21 A.M.: Injected with 2 cc. of cobra venom solution (4 mouse units), which had been irradiated with Kromayer lamp for 38 minutes, + 0.5 cc. of unirradiated cat serum.

5.30 P.M.: Very slight depression. Recovered next day.

*Mouse No. 3.*

10.22 A.M.: Injected with 2 cc. of cobra venom solution (4 mouse units) + 0.5 cc. of cat serum after the mixture had been irradiated for 38 minutes.

3.00 P.M.: Dead.

It is evident that blood serum exerts a protective action for snake venom against the destructive effect of ultraviolet radiations. Similar experiments were performed with various proportions of serum both from cats and from human beings with identical results.

Another striking illustration of the protective action of blood serum was obtained by biochemical experiments of an entirely different character. The oxidation reaction of fresh rat muscle was studied by Thunberg's method,<sup>19</sup> which need not be described in detail here. Briefly, it consists of observing the time required for the decolorization of a standard solution of methylene blue in specially constructed tubes from which all air has been exhausted. In such experiments 3 tubes were employed. In 1 tube was placed a solution of methylene blue to which a definite quantity of ground rat muscle and a small amount of physiologic saline solution were added, and the time required for decolorization of methylene blue at 37° C. was observed. This was the control experiment. In a second tube, a similar solution of methylene blue with ground muscle tissue and cat serum was placed; and 5 mg. of cobra venom, previously irradiated with a Kromayer lamp, were also added. In the third tube, an equal amount of cobra venom was introduced in a solution similar to that mentioned above, but in this case the venom used had been previously irradiated *together with* a similar quantity of blood serum. The venom irradiated alone became markedly detoxified, as indicated by the rapid decolorization of the methylene blue. On the other hand, the venom which had been irradiated together with the blood serum underwent little change and inhibited the action of the muscle oxidosis, so that no decolorization occurred. Such an experiment is illustrated by the following protocols.

A more graphic demonstration of this difference produced by irradiation of cobra venom with and without blood serum is afforded by the subjoined figures. These are kymographic tracings, showing

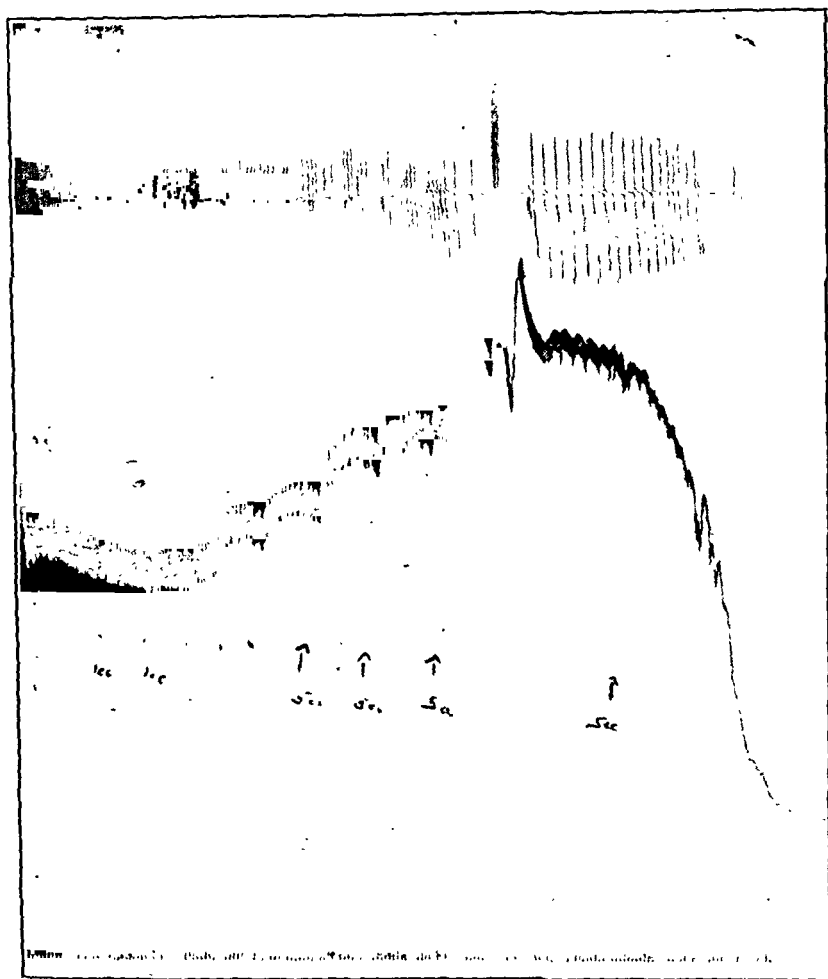


FIG. 2.—Showing effect of intravenous injection in cat of unirradiated cobra venom.

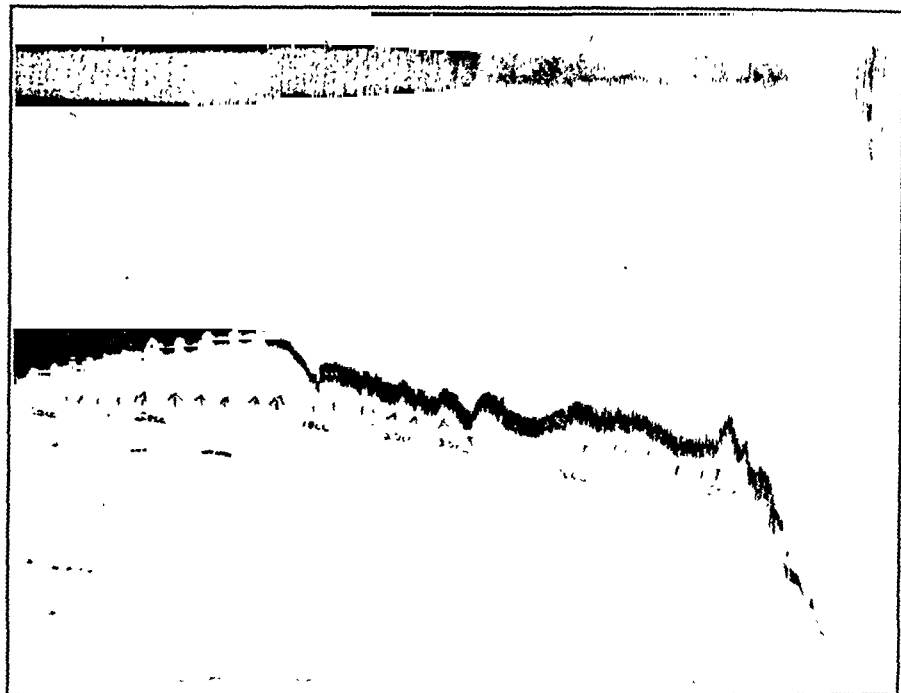


FIG. 3.—Showing effect of injections of a mixture of cobra venom and blood serum after 15-minute irradiation with Kromayer lamp.

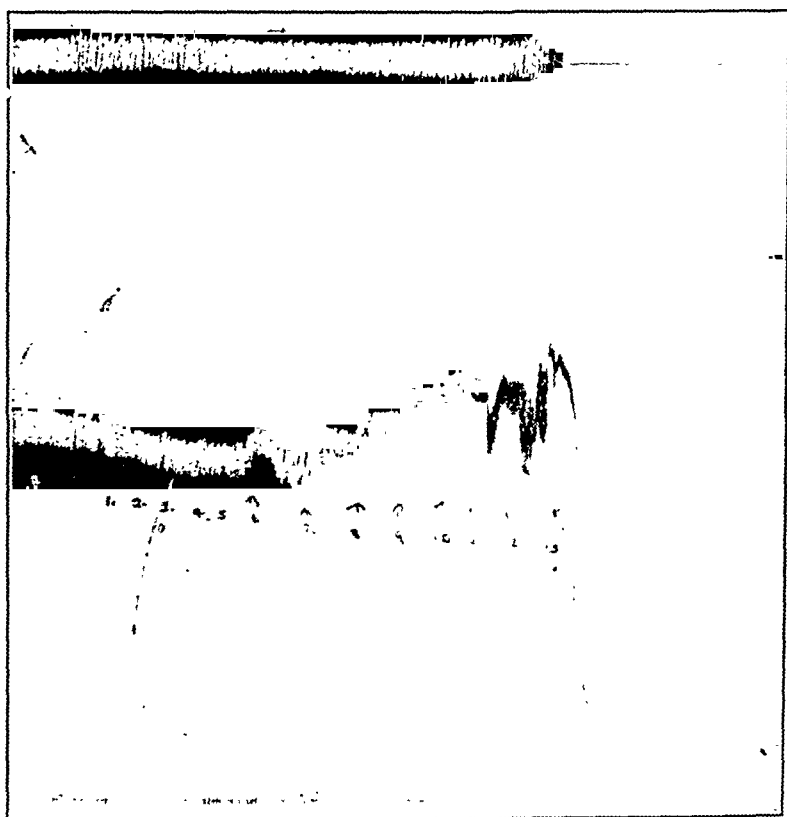


FIG. 4.—Showing effect of irradiation of cobra venom (containing no blood serum) with Kromayer lamp.

the effect of repeated, progressive injections of solutions of cobra venom, 1 to 10,000, into the femoral vein of a cat. The records indicate the effect on the respiration and circulation and also the minimal lethal dose per kilo weight required to kill the animals. It will be noted that in Fig. 2 the minimal lethal dose per kilo weight of the irradiated cobra venom injected was a little over 1 mg. In Fig. 3 is shown the effect of a similar solution of cobra venom, previously irradiated for 16 minutes by the Kromayer lamp. Here the minimal lethal dose was increased to 5 mg., indicating that marked detoxification had been produced. Fig. 4 illustrates the effect of a similar solution of cobra venom, to which a small quantity of blood serum had been added before irradiation was commenced. In this case the blood serum that had been added to the venom definitely protected it against the action of the ultraviolet rays, and the minimal lethal dose was 3.5 mg. per kilo weight of the animal.

*Experiment of October 11, 1934.*

(With Solutions in Thunberg Tubes, Each Containing 300 Mg. of Rat Muscle.)

*Tube No. 1.*

Three cc. of methylene blue solution + 3 cc. of saline + 0.5 cc. of cat serum.

Decolorized in 3 hours.

*Tube No. 2.*

Three cc. of methylene blue solution + 3 cc. of saline + a mixture of 0.5 cc. of cat serum and 5 mg. of cobra venom which had been previously irradiated with the Kromayer lamp for 15 minutes.

Oxidation completely inhibited. No decolorization in 24 hours.

*Tube No. 3.*

Three cc. of methylene blue solution + 3 cc. of saline + 0.5 cc. of cat serum + 5 mg. of cobra venom which had previously been irradiated alone with the Kromayer lamp for 15 minutes.

Decolorized in 5 hours.

TABLE 5.—EFFECT OF ROENTGEN RAYS AND RADIUM RADIATIONS ON COBRA VENOM.

Mouse No.	Dose injected, mg.	Treatment given doses of cobra venom administered.	Dead in.
1 . .	0.1	Not irradiated	1 hr., 25 min.
2 . .	0.1	Not irradiated	1 hr., 32 min.
3 . .	0.1	Exposed to Roentgen rays, 500 Roentgen units	1 hr., 33 min.
4 . .	0.1	Exposed to Roentgen rays, 500 Roentgen units	1 hr., 52 min.
5 . .	0.1	Exposed to radium radiations, 1 gm. hr.	1 hr., 24 min.
6 . .	0.1	Exposed to radium radiations, 1 gm. hr.	1 hr., 38 min.

**Effect of Roentgen Rays and Radium Radiations.** An opportunity was afforded the writer by Drs. C. F. Burnam and M. B. West, of the Howard A. Kelly Hospital, Baltimore, to treat specimens of cobra venom with Roentgen rays and radium. The results obtained are briefly summarized in Table 5. The Roentgen ray



dosage employed was 500 Roentgen units. The radium dosage was 1 gm. hour. The results obtained indicate that these powerful but very short ultraviolet rays produce little effect on the venoms exposed to them.

**Discussion.** The conclusions to which the present investigation points are clearly defined. Ultraviolet radiations were found to produce a rapid decrease in toxicity of snake venoms in aqueous solutions placed in quartz cells, the degree of deterioration being proportional to the time of exposure, as biologic experiments on both living plants and living animals indicated. In this respect the most effective ultraviolet rays were found to be those between 3000 and 4000 Ångström units. Even prolonged exposure to such longer ultraviolet rays as are filtered through a Wood filter, on the one hand, or to the shorter ultraviolet rays transmitted through a chlorin gas filter, on the other, produced little or no change in the activity of the venom solutions. Similarly, exposure to hard Roentgen rays and to radium radiations resulted in only a slight decrease in the activity of the venoms.

When snake venoms are injected into mice or rats and the animals are irradiated for curative purposes, however, the results are disappointing. The rapid onset of death indicates that there is no diminution in the virulence of the poison. Indeed, in many experiments the irradiation of animals previously injected with venom only hastened a lethal outcome. Only in exceptional cases was there any indication of a destructive action of ultraviolet rays on venom injected into the tissues of mice. In such cases the venom had been introduced in regions where absorption was poor, that is, by intradermal injection in the back. Experiments were also performed with mice to which other drugs were administered simultaneously with the venom solutions for the purpose of retarding absorption from the tissues. Such tests were made with injections of small quantities of epinephrin, which retards absorption through its powerful vasoconstricting action. Other experiments were made with injections of hypertensive solutions of sodium sulphate. In neither case was death of the animals delayed.

The great difference between the results obtained in experiments outside and inside the body, respectively, cannot be attributed altogether to poor absorption of the venoms from the tissues or to the lack of penetrating power on the part of ultraviolet rays. The experiments described above indicate definitely that certain body fluids, and particularly blood serum, exert a protective action on snake venoms against the effects of ultraviolet rays; and it is probably this mechanism which renders the therapeutic application of ultraviolet radiation futile. The most that can be expected is that such ultraviolet rays may be useful in snake poisoning when applied directly to opened wounds. When a patient is bitten by a reptile,

the usual procedure is to slash open the tissues at the seat of the bite and to apply suction or chemical antidotes to the wound. In such cases, irradiation with a mercury vapor lamp may be a useful therapeutic procedure, although it is a question whether the presence of body fluids may not interfere with the effectiveness of the ultraviolet rays. Irradiation of venom solutions in quartz containers may also prove to be a useful method of attenuating the poisons for the purpose of injection in suitable clinical cases where therapeutic administration of snake venoms is indicated.

**Summary.** 1. Exposure of snake venoms in solution to radiations of mercury vapor lamps produces progressive decrease in toxicity, as indicated by pharmacologic tests on living plants and animals.

2. The ultraviolet rays most effective in this respect lie in the region between 3000 and 4000 Ångström units, the longer and shorter ultraviolet rays being less effective.

3. Snake venoms exposed to Roentgen rays and radium radiations undergo but little change in toxicity.

4. Mice exposed to ultraviolet rays after previous injection of snake venom exhibit no diminution of susceptibility to this toxin and usually succumb more quickly than unirradiated animals injected with venom.

5. The difference between the effects produced by ultraviolet rays on snake venoms *in vivo* and in quartz containers, respectively, is due primarily to the protective action exerted by blood serum.

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## EFFECTIVE TREATMENT OF ARACHNIDISM BY CALCIUM SALTS.

### A PRELIMINARY REPORT.

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INVESTIGATION of the treatment of the black widow spider (*Latrodectus mactans*) bite has been going on since the serious results of the bite have been recognized, probably since the beginning of the 18th century. During the past 10 years this investigation has been more scientifically thorough and extensive; but it certainly has not produced any definite and easily accessible therapeutic measure which can be depended upon in all cases for the immediate and lasting relief of the extreme pain which most of the affected patients suffer. The search is indicated not only because of the severity of the pain and the mortality, but because of the relatively widespread existence of this spider. Cases have been reported in 32 states of this country, mostly in the southern half, also in South America and Australia, and with less frequency in other parts of the world.<sup>1,2</sup>

In the past, numerous therapeutic agents have been used, some more or less rational, but mostly without any such basis. Bogen<sup>3</sup> lists 60, such as morphin, whiskey, spirits of ammonia, atropin, magnesium sulphate, strychnin, calomel, castor oil, iodin, salicylates, hot applications, enemas, etc. In our experience, as in that of others,<sup>1,4-17</sup> morphin has been used with indifferent success when administered to adults even in large doses. The fallacy lies in the fact that it has no effect on the seat of the pain itself, but affords variable degrees of relief only by its depressant action on the central nervous system. Spinal fluid pressure is known to be increased but withdrawal of fluid has been found to give quite inconstant results.<sup>1</sup> Magnesium sulphate, intravenously, which probably acts by decreasing the cerebrospinal fluid pressure, has been used with more or less success, but the relief obtained is neither immediate nor complete.<sup>1,4</sup> Furthermore, considerable technical difficulty would be experienced in its administration to infants or small children. Convalescent serum<sup>1,3,8,24</sup> has been demonstrated to have little or no effect on victims of the venom.

The serum must be administered immediately after the patient has been bitten, which is impracticable, and one<sup>2</sup> of the proponents of its use has admitted that the course is unaltered except for being shortened by a day or two. Further discussion seems unwarranted for we have reviewed a large portion of the literature<sup>3,5-23</sup> dealing with cases of *Latrodectus mactans* bite and find that no treatment is of particular value.

We have attempted to develop some simple form of therapy which will insure early and lasting relief from the excruciating pain present in this condition.

The active principle of the venom has not, as yet, been definitely determined, but, as to its mode and place of action, it is quite generally accepted that the toxin directly stimulates the myoneural junctions or that it acts on the nerve endings.<sup>2,8,13,25</sup> To find a type of therapy which would have a direct depressant effect upon these structures would be ideal. As calcium apparently depresses the neuromuscular junctions<sup>26</sup> in muscle or is depressant to most nervous and muscular functions,<sup>27</sup> we selected calcium salts for the treatment of this condition.

We found that intravenous injections of 10% calcium chlorid gave instantaneous and prolonged relief of the pain, and at the same time produced immediate relaxation of the muscle spasm so commonly seen in these patients. However, calcium chlorid is not given thus without considerable danger. Its necrotic action on tissue outside a vein is only too well known. This danger is greatly magnified when its use is attempted in the treatment of children. Therefore, calcium gluconate (10 cc. of 10% solution, intravenously), which does not have this objectionable feature, was used and found to produce equally as spectacular results as the calcium chlorid. The intramuscular route, advisable for children, gave relief within a minute's time. Calcium lactate orally was ineffective as far as determined, probably because of its incomplete and slow absorption.

**Case Reports.** CASE 1.—C. W., a white male, aged 16, was admitted at 6 P.M., October 26, 1934, having been bitten at 3 P.M. in the right shoulder region while lying under a car upon ground thickly covered with grass and weeds. The bite produced a sharp sting. About  $\frac{1}{2}$  hour later there was dull pain in the right shoulder, gradually becoming more severe and spreading to the chest and abdomen and then to the legs. Examination revealed the patient rolling from side to side because of the excruciating pain. The forehead was covered with perspiration. A red area, about 1 cm. in diameter, was visible at the site of the bite. Both pupils were dilated. Blood pressure was 160/70. Heart and lungs were normal. The abdomen revealed board-like rigidity, but no tenderness. Much pain was complained of in the extremities, but no tenderness or spasticity was elicited. Serological study was negative. At 6.20 P.M., before an intravenous injection of 20 cc. of 10% calcium chlorid could be completed, the pain and muscle spasm had entirely disappeared. At 10.45 P.M., pain returned in the legs and another 20-cc. intravenous injection was given. The next morning, at about 9 o'clock, the urinary bladder was found distended

two-thirds of the way to the umbilicus, but the patient soon voided without catheterization. The treatment was repeated at 2 P.M. and at 9.30 P.M. and on October 28 at 10 A.M., because of the return of pain in the lower extremities. Thereafter, until discharge, at 4 P.M., October 30, there was no further pain. Unfortunately, the patient did not search for the suspected black widow spider.

CASE 2.—C. G., a Mexican male, aged 16, was bitten on the scrotum at noon of November 1, 1934, while seated in an infrequently used toilet in the rear of a garage. Upon feeling the sting, the boy reached for the scrotum and pulled forth a spider which was later identified by a physician as being a black widow. Soon afterward, pains were experienced in the abdomen and back and then "everywheres," and later vomiting ensued. The patient could not sleep and was admitted, November 2, 1934, 9.30 A.M., still complaining of marked pain. He was sweating profusely; his eyes red and swollen. Heart and lungs were normal. The abdomen was rigid, but not board-like. At 11 A.M., 20 cc. of 10% calcium chlorid was given intravenously and the pain disappeared within 30 seconds. At 5.30 P.M., because of pain in the throat, 10 cc. of 10% calcium gluconate was administered intravenously and was repeated at 10 P.M. with instant relief. Examination of the throat before giving medication revealed no lesions. On the second day at 9 A.M., 5.45 P.M. and 8.30 P.M. and on the third day at 9.15 P.M., 10 cc. of 10% calcium gluconate was given intramuscularly on the return of pain. It was found that, except for a slight delay, calcium gluconate by this route relieved the pain as effectively as when given intravenously. On the second and third days, calcium lactate, 120 gr., twice daily, was given orally but was discontinued because of no apparent results. On the second day, 9 hours after any intravenous or oral administration of calcium, the blood was found to contain 12 mg. of calcium per 100 cc. of serum. Serologic studies were negative. The patient was discharged, November 6, relieved of all symptoms.

CASE 3.—H. T., a white male, aged 36, on November 18, 1934, about 7 P.M., on his back porch, felt something crawl down his back, and then experienced a burning pain in the right scapular region. In 10 minutes the upper back felt numb, followed by a tight feeling about the chest, and in turn severe lumbar pain, moderate abdominal pain and pains in the legs. The spider was later brought to us and identified as a black widow. On admission, at 10.30 P.M. of the same day, the patient was experiencing excruciating pains in the lumbar region and lower chest. The blood pressure was 150/100. The heart and lungs were normal. There was rigidity of the abdomen, but no tenderness. Serologic study was negative. When seen the next day, the man's pains were not severe, but at 6 P.M. he was found tossing and crying because of pain in both lower extremities and in the abdomen. Ten cc. of 10% calcium gluconate were given deep in the gluteal region, and within 1 minute the pain had entirely disappeared. Thereafter the pains were limited to the legs, but were not at all severe. However, another injection was given at noon, November 21, with total relief of the pain until discharge on November 23.

CASE 4.—C. H., a white female, aged 69, was bitten by a spider about 8 A.M., on November 6, 1934, on the back of the left hand while handling a pair of stockings she had just removed from her clothesline. Without any coaching whatever she described the creature, giving the characteristic features of a black widow spider. Almost at once there was pain in the hand which continued. An hour later, there was also pain in the axilla which became progressively worse. On admission, at 10.30 A.M., the patient did not seem to be in great pain. The blood pressure was 170/85. There was swelling and redness of the dorsum of the left hand and tenderness in the muscles of the arm, shoulder and pectoral regions, without any rigidity. The heart, lungs and abdomen were normal. The blood calcium

was 10.1 mg. per 100 cc. of blood serum and the blood serologic studies negative. By 2 P.M. the pain had increased so that the patient was found sitting on the side of the bed holding the left side of her chest and the left arm, having an agonizing expression. Calcium gluconate, 10 cc. of 10% solution, was given intramuscularly with almost immediate relief of the pain, although tenderness remained. There was no further pain and the redness and swelling of the hand gradually subsided before discharge on the morning of November 10.

**CASE 5.**—A white male, aged 28, was bitten by a black spider, on November 6, 1933, on the scrotum while tearing down an old barn. About 2 hours later he developed nausea, vomiting, profuse perspiration, excruciating generalized abdominal pain, pains in the thighs, legs, arms and forearms, and a feeling of tightness and suffocation about the chest and throat. He was unable to speak because of "tightness" in the masseter muscles. Admitted to St. Vincent's Hospital, at 9 P.M., November 7, 30 hours following the bite, he was found screaming with pain, and thrashing and rolling about the bed. The skin was hot and moist. Blood pressure was 160/95. The pulse was rapid but of good quality; temperature, 101° F.; respirations, 30. There was board-like rigidity of the abdomen, but no tenderness. The reflexes could not be accurately determined because of the extreme restlessness. The white blood count was 30,000, with 80% neutrophils. At 10 P.M., a 10-cc. ampule containing 1 gm. of calcium chlorid was given intravenously with immediate relief of the pain and total relaxation of the spastic muscles. Ten minutes later, the patient was sitting up in bed, smoking and drinking and complaining only of some aching in the feet and throat. Morphin sulphate,  $\frac{1}{4}$  gr., was given hypodermically with sleep following. Because of a return of the pain, 7.30 A.M., the following day, another ampule of calcium chlorid was given with the same favorable results. Symptoms again returned, 9 P.M., November 9, when 1 gm. of calcium gluconate was taken orally followed by a hypodermic of morphin with relief of pain in 15 minutes. Three hours later it was necessary to repeat these same drugs and again at 2 P.M., November 10, with relief of pain 15 minutes later each time. The patient was discharged that evening symptomless.

**Comment.** It is evident from the cases cited that the calcium salt was responsible for the relief and that the time required depends on the method of administration, the intravenous method giving the most rapid results, and the intramuscular only slightly slower. In spite of the disappearance of the pain in Case 5 when calcium was given by mouth, we still believe it is not a desirable, and in fact a futile, route of administration, as shown in Case 2. In Case 5 morphin was given in conjunction.

The observation in Case 4 indicates that the symptoms in this malady are not due to a lowered calcium as in tetany for the serum calcium was within normal range.

**Conclusions.** 1. *Latrodectus mactans* and victims of their bite are common enough throughout the world to warrant search for a suitable form of therapy.

2. No remedies have heretofore been reported which produce certain, immediate and prolonged relief of pain.

3. Calcium depresses the myoneural junctions, which, it is believed, are stimulated by the venom.

4. Calcium in the form of calcium gluconate is chosen because of its ease of administration to children by the intramuscular route

and because it is practically without hazard when given intravenously.

5. A limited number of cases are reported to show its efficacy in producing real, immediate and prolonged relief.

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(Titles have been omitted for sake of brevity.)

## HYPOPROTEINEMIC NEPHROSIS AND ITS TREATMENT WITH ACACIA.

### REPORT OF TWO "CURED" CASES.

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VARIOUS attempts have been made to classify lipoid nephrosis as a renal disease; but lipoid nephrosis will be satisfactorily defined and classified only after its ultimate etiology and pathologic physiolog-

ogy are fully known. Clinically, this condition is easily recognized; nevertheless the diagnosis of lipid nephrosis should be made with the reservation that some of the cases so diagnosed will prove, in the last analysis, to be cases in which the kidneys show insignificant pathologic lesions. This nephrosis syndrome, characterized by edema or anasarca, may also be induced by a hypoproteinemia following protein starvation and protein loss as in chronic diarrhea. Leiter<sup>1</sup> estimated that true lipid nephrosis occurs in 1 to 5% of all non-suppurative renal diseases.

*Diagnostic Criteria.* 1. History of onset with acute infection. Nephrosis generally occurs in the young.

2. Severe albuminuria, oliguria, ability to concentrate urine, absence of hematuria.

3. Edema or anasarca.

4. Lipemia; hypercholesterolemia.

5. Low serum albumin, high serum globulin, a reversal of the normal albumin-globulin ratio of the blood serum. Serum albumin below the critical level at which edema begins.

6. Doubly refractile lipoids in the urine.

7. Clear transudate in extremities; opaque, milky ascitic fluid.

8. Systemic (pneumococcic) infection in the terminal stages of the disease.

*Pathology.* Epstein<sup>2</sup> has designated nephrosis as a "diabetes albuminuricus," emphasizing the metabolic origin of this condition. He explained the edema on the basis of reduced plasma protein. Leiter<sup>3</sup> contrasts and correlates nephrosis with chronic glomerulonephritis. His experimental studies led him to the conclusion that loss of serum proteins with its resultant hypoproteinemia is the underlying cause of the edema. Amberg<sup>4</sup> is of the opinion that the comparatively slight structural changes in the kidneys in chronic nephrosis exclude it from being classified with renal disease, and that depletion in blood proteins alone is not the underlying cause of the edema. He believes that there must be certain chemical disturbances behind all this. Bell,<sup>5</sup> leaning upon Senator's conception of glomerulonephritis, looks upon chronic nephrosis as a nephrotic type of glomerulonephritis, and he believes that the primary cause in both nephrosis and nephritis resides in toxic injury to the renal capillaries. Hitzrot and Read<sup>6</sup> see very slight or no relationship between nephrosis and glomerulonephritis. Moschcowitz<sup>7</sup> holds that "nephrosis cannot be classified as a disease because it has multiform backgrounds in morbid anatomy," and that the fundamental cause of the edema in these conditions is hypoproteinemia.

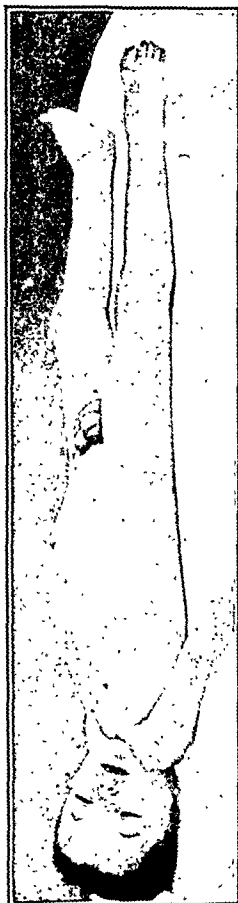
After due consideration of these views, some of which are conflicting, it is perhaps best that, for the present, the clinician look upon nephrosis simply as a well-defined clinical syndrome. It is evident that the glomeruli at times do show histologic changes. It



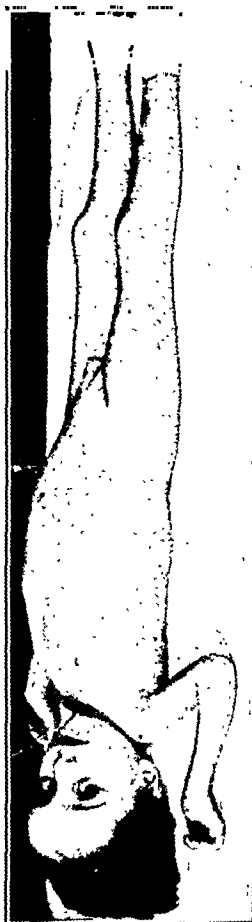
is likewise true that such changes are probably not more extensive than could be found in other tissues in a well-marked case of this disease state. It should be recalled here that edema of itself is not a sequel to injury or destruction of renal tissue.



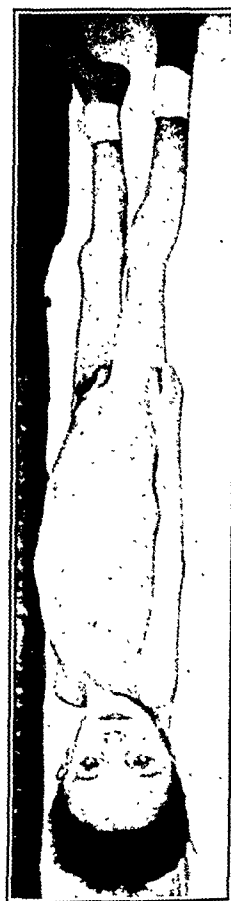
On discharge.



Before anecia.



Two days after anecia.



Three weeks after anecia.

On the whole, available evidence favors the view which has been acceptable to Epstein, Leiter, Moschowitz and others that loss of serum protein through severe albuminuria causes a fall in osmotic

pressure with resulting edema. Leiter<sup>1</sup> and later Moschowitz<sup>7</sup> noted the fact that in hypoproteinemia it is loss of the albumin fraction which is important in edema production. The part played by the cell is not yet understood, neither are the chemical or physico-chemical changes that the cell must undergo to permit the change in osmotic pressure.

**Present Experience.** Our main interest here is in the striking results obtained in the treatment of 2 patients by intravenous injections of acacia, as advocated in this country by Hartmann, Senn, Nelson and Perley.<sup>8</sup> Acacia intravenously raises the colloidal osmotic pressure of the blood plasma toward the normal. After a preliminary smaller dose, it may be given to establish a 2% concentration in the plasma, which concentration is obtained by administering 1 gm. per kilo body weight. We used a 30% solution of acacia with 4.5% sodium chlorid solution, which should be a clear pale yellow. Darker solutions may cause reactions and should be avoided. This acacia solution is diluted with normal saline to a total volume of 500 cc. and injected slowly.

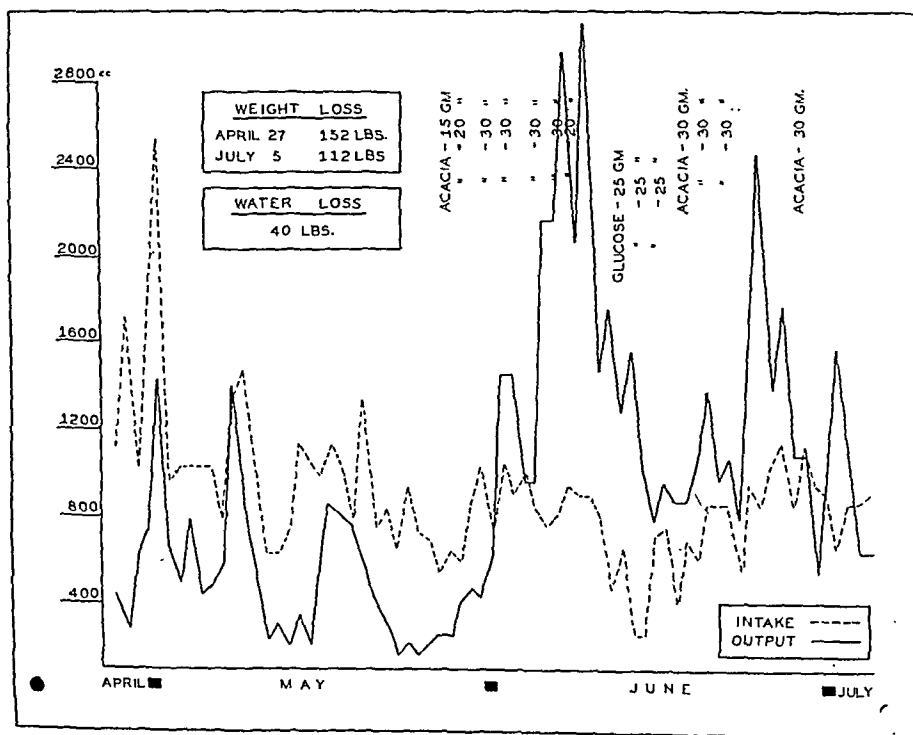


CHART 1.—Intake and output—Case 1.

**CASE 1.**—(Barach.) Mary Louise S., aged 20, admitted to the hospital, April 26, 1933. Her family history was negative. Her past history included an appendectomy 5 years ago, tonsillectomy 4 years ago and menstrual irregularity for 1 year.

*Present Illness.* The patient was diagnosed and treated as a case of nephritis, with a heavy cloud of albumin, for 1 year. Six months ago, following an attack of "influenza," she developed edema of the ankles and feet which gradually culminated in a generalized edema. She had been confined to bed since that time. For the past 4 months, she has had recurring nausea and vomiting, orthopnea, facial edema and anasarca. The case seemed quite typical and a clinical diagnosis of chronic nephrosis was made at the time of the consultation with her attending physician. Following this, she was hospitalized.

*Clinical Findings.* There was a generalized anasarca, including edema of the face and arms, ascites and massive edema of the lower extremities. There was oliguria and severe albuminuria. The serum albumin and total serum protein were low while the serum globulin was high. Whereas edema may develop when the daily loss of protein reaches 1 gm. per liter per day,

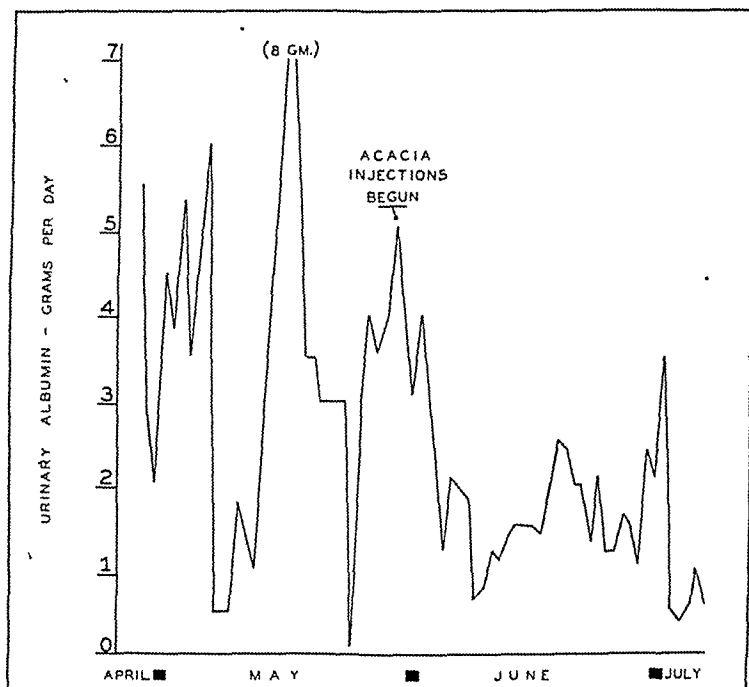


CHART 2.—Urinary albumin—Case 1.

this patient's loss of protein up to the time of the acacia varied between 1.5 and 8 gm. daily. Hypercholesterolemia was marked. At one tap, 3100 cc. of milky ascitic fluid were obtained and 3 weeks later 6100 cc. were removed. A secondary anemia was found. Blood chemistry, other than serum protein, was normal. Urinary urobilinogen output was high and glucose tolerance was normal. Figure 1 gives the detailed studies of this case.

*Treatment—Diet.* To meet the caloric requirement, a diet of carbohydrate, 120 gm., protein, 52 gm., and fat, 70 gm., was ordered, with low salt. The patient was kept on this diet for 1 month. During the first month there was no improvement. A Carrell diet consisting of 800 cc. of milk daily was instituted for 5 days. This was followed by oliguria, her condition was aggravated and we abandoned the Carrell diet. Following this, the patient's diet was adjusted to 1.5 gm. protein per kilo body weight.

Half of this protein was given in the form of gelatin. No effects were noted over a period of 4 weeks.

*Medication.* Desiccated thyroid extract (1 to 5 grains, t.i.d.) was not effective and was discontinued. Potassium bitartrate in large and small doses was not effective. Daily injections of glucose, 10 to 25%, intravenously, did not produce diuresis; its effects were neither good nor bad. Calcium lactate was given by mouth and seemed ineffective. Magnesium sulphate ( $\frac{1}{2}$  ounce daily) produced free bowel movements with elimination of a certain amount of liquid.

*Acacia.* None of our therapeutic measures were effective up to the time of the first injection of acacia. Altogether 11 injections of acacia were given, making a total of 295 gm. in 4 weeks. One intravenous injection of 15 gm., 2 of 20 gm. and 8 of 30 gm. each were given at 1- or 2-day intervals. For the anemia, weekly injections of liver extract intramuscularly seemed to induce a favorable response.

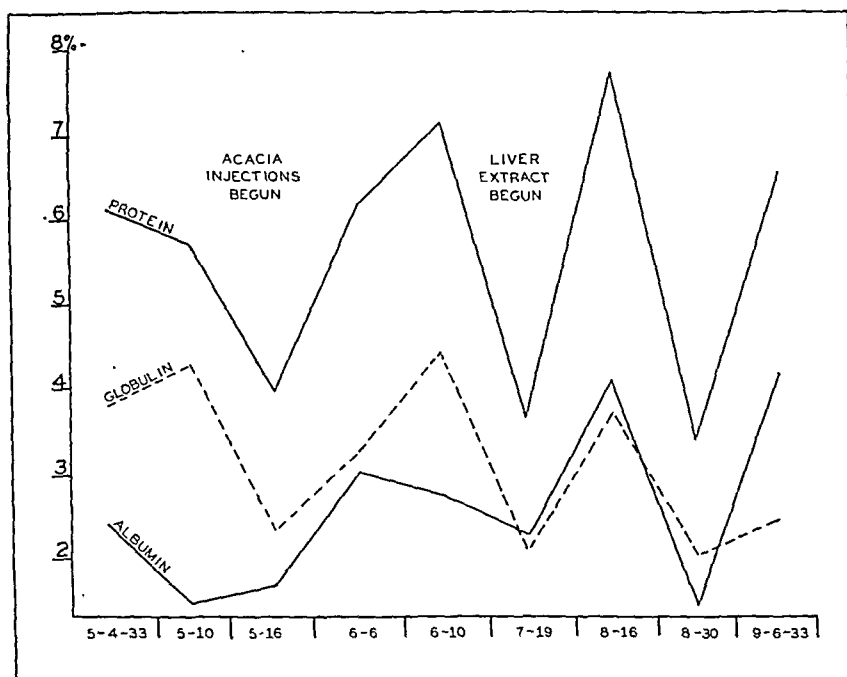


CHART. 3—Serum protein—Case 1.

*Course and Summary.* We have here a typical case of chronic nephrosis which responded satisfactorily only after intravenous injections of acacia were begun. Diuresis was striking, as is shown in Chart I. For the first time in 7 months, the patient showed clinical improvement. The patient received in all 11 intravenous injections (295 gm.) of acacia during her stay of 72 days in the hospital. During this time there was a loss of 40 pounds in body weight, most of which was water loss. When she was first allowed out of bed there was still considerable edema at the ankles, but this subsided gradually. Six weeks after she left the hospital, there was no visible edema and her general condition was good. The urine still showed a cloud of albumin, otherwise she showed evidences of a clinical recovery.

On December 1, 1934, 2½ years after the beginning of this disease and

1½ years after the acacia injections were begun, this patient is to all appearances in good health. She married 7 months ago and is now 6 months pregnant. She is in good health and there is no edema. Her serum protein is 9.25%, serum albumin, 5.52%, and serum globulin, 3.73%. The urine is negative for albumin. All of this is evidence of a return to normal.

TABLE 1.—PROTOCOL OF CASE 1.

	4/26.	5/4.	5/10.	5/16.	5/20.	6/6.	6/10.	6/20.	7/19.	8/9.	8/16.	8/30.	9/6.
Body weight (pounds)	152	151	...	...	147	140	121½	115	120	119½	119	119½	124½
Serum protein (%)	..	6.09	5.67	3.90	...	6.10	7.06	...	3.59	...	7.65	3.31	6.50
Serum albumin (%)	..	2.35	1.40	1.61	...	2.93	2.69	...	2.00	...	4.01	1.36	4.10
Serum globulin (%)	..	3.74	4.27	2.29	...	3.17	4.37	...	1.59	...	3.64	1.95	2.40
Blood urea (mgm.)	..	...	...	...	...	...	10.5	...	...	...	...	...	...
Blood N.P.N.	28.5	28.5	...	...	...	...	29.6	29.6	...	...	...	...	31.4
Blood creatinin "	2.2	...	...	...	...	...	1.8	...	...	...	...	...	1.6
Blood sugar "	115	65	...	...	...	...	...	90.9	...	...	...	...	87
Blood chlorid "	500	...	...	...	...	...	663	534	...	...	...	...	478.5
Blood cholesterol "	..	...	428.6	428.6	...	...	279	262	...	...	...	...	300
Blood calcium "	..	...	...	...	7.2	...	...	...	...	...	...	...	9.7
Icterus index	..	21.4	...	...	...	...	...	...	...	...	...	...	13
Hemoglobin (%)	80	...	...	...	52	56	...	63	55.8	84.1	...	87.2	...
R. B. C. (millions)	4.1	...	...	...	2.52	2.94	...	6.25	2.9	4.38	...	5.08	...
W. B. C. (thousands)	11.1	...	...	...	5.2	7.0	...	9.6	5.8	...	...	...	...
Urinary urea (gm. per liter)	4	...	...	...	...	9	...	...	...	...	...	13.8	...
Urinary N.P.N. (gm. per liter)	1.6	...	...	...	...	6.05	...	...	...	...	...	...	...
Urinary chlorid (gm. per liter)	..	...	...	...	...	...	...	...	7.0	6.5	...	15.0	...
Urinary albumin (gm. per 24 hours)	5.5	3.5	1.8	8.0	3.0	1.9	1.2	2.0	4.5	7.0	5.2	5.6	3.0
P. S. P. test	76%	...	...	...	...	...	...	...	...	...	...	...	...
Glucose tolerance	..	...	...	...	...	...	...	Norm.	...	...	...	...	...

CASE 2.—(Boyd.) Robert O'M., aged 4 years, 3 months, entered the Children's Hospital on August 11, 1932. There was a history of rickets and bronchopneumonia at 7 months and tonsillectomy at 3 years and 3 months of age.

*Present Illness.* At the time of his tonsillectomy, the family physician had diagnosed kidney trouble, looking forward to improvement after the tonsillectomy. Six months later there was morning puffiness under the eyes. This became worse and generalized edema gradually developed. One year after the albuminuria was first discovered, there was ascites. At this time the patient was hospitalized.

*Clinical Findings.* At the time of entrance to the hospital, there was weakness, anorexia and swelling of the abdomen, genitalia and lower extremities. The blood pressure was 103/70, eye grounds were negative and the sinuses, ears, nose and throat were negative. The Wassermann reaction was negative. The urine showed a heavy cloud of albumin with casts and doubly refractile lipoids. His blood chemistry was negative except for serum protein, as shown in Table 2. There was anemia and with this a periodic leukocytosis.

*Treatment—Diet.* The diet was high in protein. Fluid restriction had no beneficial effects.

*Medication.* Hot and dry packs were ineffectual. Magnesium sulphate and jalap were used for catharsis. Thyroid (½ grain, t.i.d., for 5 to 6 weeks) was not effective. Urea (in doses of 5 to 15 grains, t.i.d.) was given throughout the hospital stay. Calcium gluconate was given, 10 cc., intravenously, for 4 injections. Salyrgan was given in doses of ½ ampule, but the results were not favorable. An autogenous vaccine of a non-hemolytic streptococcus was cultured from the urine. This was inoculated into a suitable

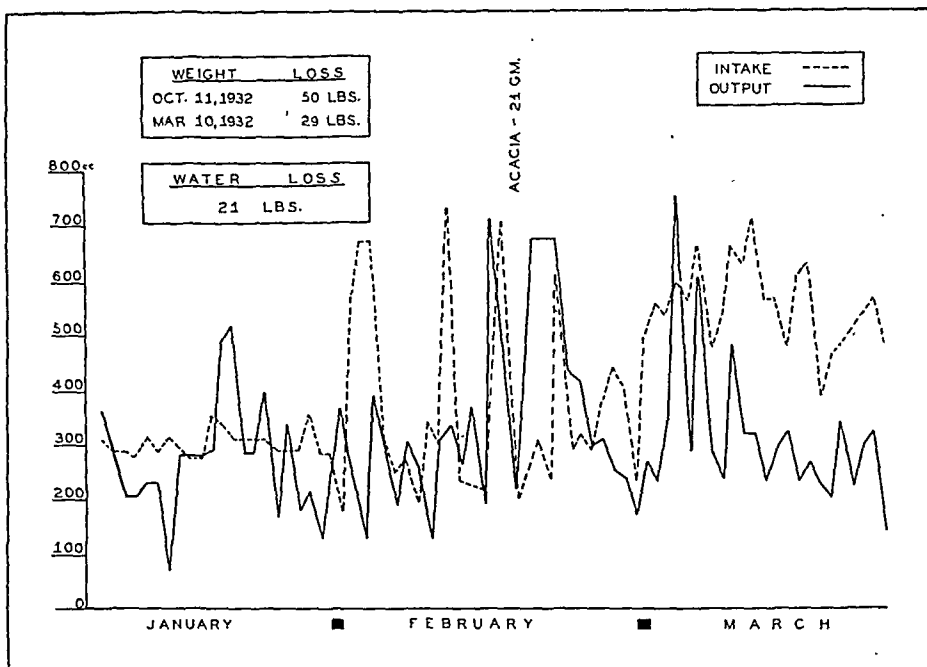


CHART 4.—Intake and output—Case 2.

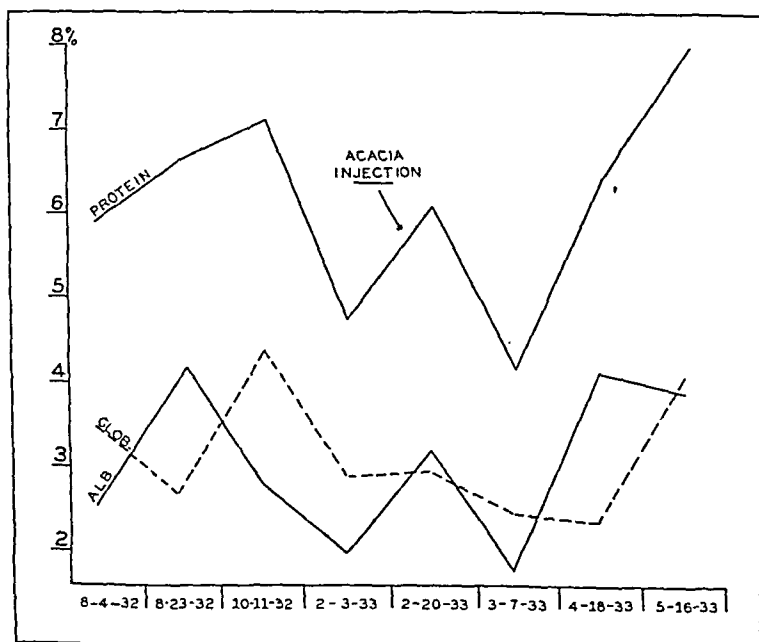


CHART 5.—Serum protein—Case 2.

donor and several transfusions given to the patient. It may be said that none of these therapeutic measures produced a striking result.

*Acacia.* On February 18, 1933, 7 months after entrance into the hospital, 21 gm. of acacia was given intravenously. Following this there was a striking diuresis which was followed by daily improvement in the patient's general condition. Up to this time the patient had been in the hospital 7 months without visible improvement regardless of the various treatments attempted.

*Course and Summary.* Three months after the acacia injection, he was well enough to be discharged from the hospital. On December 8, 1934, almost 22 months after the acacia injection, the patient is living a normal boy's life and is apparently in good health. His urine still shows some albumin but his serum protein is 8.37% and his general condition indicates a clinical recovery.

TABLE 2.—PROTOCOL OF CASE 2.

	7/7.	7/14.	8/4.	8/23.	9/20.	10/11.	11/1.	1/11.	2/3.	2/20.	3/7.	4/18.	5/16.	10/16.
Body wt. (lbs.)	50	...	...	...	...	...	...	50	45	35½	29½	...	...	42
Serum protein	...	...	5.85	6.58	...	7.05	...	...	4.70	5.04	4.10	6.38	7.95	7.65
Serum albumin	...	...	2.45	3.98	...	2.75	...	...	1.90	3.14	1.70	4.08	3.90	4.00
Serum globulin	...	...	3.40	2.60	...	4.30	...	...	2.80	2.90	2.40	2.30	4.05	3.65
Blood urea	...	...	11.6	7.6	...	...	...	...	...	...	...	...	...	...
Blood N.P.N.	46	42.8	36.1	30.6	25.0	...	...	...	35.0	...	27.3	42.8	35.5	...
Blood creatinin	1.4	1.7	...	1.0	...	...	...	...	1.0	...	...	...	...	...
Blood sugar	...	117	...	...	...	96.1	...	...	...	...	...	...	...	...
Blood chlorids	...	515	...	...	...	...	...	...	...	...	...	...	...	...
Hemoglobin, %	77	...	83	...	77	...	60	91	...	55	50	...	64	78.9
R.B.C. (m <sup>3</sup> 's)	4.2	...	4.25	...	3.95	...	3.15	4.65	...	2.9	2.7	...	3.35	4.65
W.B.C. (th's/d)	16.2	...	12.2	...	9.9	...	12.1	9.1	...	32.8	12.8	...	9.6	13.3
P.S.P. test	Trace	...	...	...	...	...	...	...	...	...	...	...	...	...
Doubly refractile lipoids	...	...	...	...	...	...	11/3 11/4	...	...	...	...	...	...	...
Urinary alb.	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++	++	0.23

**Summary and Conclusions.** A case of chronic lipid nephrosis in a young woman, aged 20, and one in a boy, aged 4, are reviewed. Neither patient showed evidences of improvement until acacia was given intravenously. One case received 11 injections, totaling 295 gm. acacia, the other required only 1 injection to start the diuresis and bring about a clinical recovery. In both patients there was a striking diuresis following the acacia injections. Systemic reactions from the acacia injections were mild and without ill-effects. Intravenous injections of acacia as used here have produced the most striking therapeutic effects that we have ever seen in chronic nephrosis.

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# THE EFFECT OF EQUIVALENT AMOUNTS OF DEXTROSE AND STARCH ON GLYCEMIA AND GLYCOSURIA IN DIABETICS.\*

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THE question of the extent of glycemia and glycosuria produced in patients suffering from diabetes mellitus by the ingestion of dextrose and of an equivalent amount of starch has received but little study.

Allen,<sup>1</sup> in a paper on the effects of carbohydrate diets on diabetes, makes the following statement: "Numerous observations have made it evident that glucose brings on glycosuria and diabetes more actively than starch. The difference is not merely one of quantity, for the addition of 50 or 100 gm. of glucose is sometimes effective when no amount of bread feeding avails for glycosuria. The reason for the readier glycosuria from glucose lies evidently in its quicker absorption, and if distributed in sufficiently small doses throughout the day it would presumably be assimilated as well as starch, as Klemperer showed in human patients. The most important point here is that the sudden glucose flood with its attendant glycosuria is more injurious to the pancreatic function than the more gradual and prolonged labor imposed by starch. It may thus be inferred that sugar is a more dangerous food for human beings with any predisposition to diabetes than is starch." He states further: "In the early stage glucose is more powerful than starch in producing diabetes, and animals which are progressing toward complete recovery on starch diet can be sent into hopeless diabetes by admixture of glucose."

As far as normal individuals are concerned, Howell<sup>2</sup> states that the more slowly converted starch may be eaten in larger amounts than the rapidly absorbed sugar without raising the percentage of blood sugar above normal. He further points out that during the 4 or 5 hours required for starch digestion the entire quantity of blood in the body goes through the mesenteric arteries many times, and it is probable that even in the portal vein the quantity of sugar is never much above normal. As any small excess is largely held back by the liver cells, systemic hyperglycemia does not occur.

It has been shown by MacLean,<sup>3</sup> and also by Rosenthal and Ziegler,<sup>4</sup> that the rise in the concentration of the blood sugar in

\* Aided by a grant from the Committee on Scientific Research of the American Medical Association.



normal individuals after the ingestion of equivalent amounts of dextrose and starch is identical.

In this paper the results of experiments on the influence of the ingestion of dextrose and of an equivalent amount of starch on glycemia and glycosuria in patients suffering from diabetes mellitus will be reported.

**Method.** Experiments were performed on 21 diabetics. To 10 of them 100 gm. of dextrose, in a 20% aqueous solution, were given in the morning after a fast of 14 hours. Blood (venous) specimens were taken at the "fasting level" immediately before ingestion, 45 minutes and 2 hours after the ingestion of dextrose. The sugar content of the blood was determined by the Folin-Wu method. The urine was collected at the end of 45 minutes and 2 hours after ingestion of the dextrose, and its sugar content determined by Benedict's method.

Two days later, also in the morning after a fast of 14 hours, 90 gm. of starch\* were given. The blood was taken and the urine collected at the same periods as when dextrose was given. In the interval between tests the patients were on their customary diets. Those who had been taking insulin continued to do so.

The same procedure was carried out on 11 other diabetics with this important difference, namely, that the starch was given first and the dextrose 2 days later.

TABLE 1.—CONCENTRATION OF DEXTROSE IN THE BLOOD AND QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 100 GM. OF DEXTROSE AND 90 GM. OF STARCH.

(In this series of cases the dextrose was given first and the starch 2 days later.)

Case No.	Blood sugar (mg. per 100 cc. of blood).						Urine sugar (gm.).					
	Fasting level.		45 minutes post cibum.		2 hours post cibum.		0 to 45 minutes post cibum.		45 minutes to 2 hours post cibum.		Total, 0 to 2 hours post cibum.	
	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.
1 . . .	333	326	508	500	576	454	10.8	11.6	32.0	24.8	42.8	36.4
2 . . .	306	375	460	546	546	508	2.7	11.3	21.1	19.6	23.9	30.9
3 . . .	375	395	500	600	556	682	4.8	5.5	13.5	22.7	18.3	28.2
4 . . .	214	230	344	374	410	380	5.0	6.8	13.2	16.0	18.2	22.8
5 . . .	170	196	208	272	410	384	0.12	0.67	2.9	5.6	3.0	6.2
6 . . .	272	222	460	405	556	390	4.2	2.8	15.7	13.9	19.9	16.7
7 . . .	294	303	468	405	680	600	5.7	5.3	11.5	12.9	17.2	18.2
8 . . .	300	332	468	500	556	546	5.2	6.0	13.5	16.3	18.8	22.4
9 . . .	272	318	566	422	468	492	3.1	1.4	13.8	15.0	16.9	16.4
10 . . .	221	280	404	428	600	566	1.7	2.0	14.1	14.3	15.0	16.3
Means . .	275.7	297.7	438.6	445.2	535.8	500.2	4.34	5.34	15.14	16.12	19.48	21.46
Difference between means	22.0		6.6		35.6		1.0		0.98		1.98	

\* The elementary formula for starch is  $(C_6H_{10}O_5)_n$  with a molecular weight of  $n(162)$ . The molecular weight of dextrose  $(C_6H_{12}O_6)$  is 180. The complete hydrolysis of 90 gm. of starch yields 100 gm. of dextrose. In this experiment the starch was given in the following form:

	Total, gm.	Carbohydrate, gm.
Potato . . . . .	150	30.0
Barley . . . . .	30	22.4
Rice . . . . .	30	22.4
Bread (toast) . . . . .	30	15.0
		89.8

The starch was thoroughly cooked or baked, for raw starch is hardly acted upon by either salivary or pancreatic diastase.

*Analysis of Results.* In Table 1 are recorded the concentrations of blood sugar and amounts of dextrose in the urine after the ingestion of equivalent amounts of dextrose and starch, where the dextrose was ingested first. Statistical analysis\* (Table 1a) does not

TABLE 1a.—DIFFERENCES IN THE CONCENTRATION OF DEXTROSE IN THE BLOOD AND THE QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 100 GM. OF DEXTROSE AND 90 GM. OF STARCH.  
(Where dextrose is ingested first and starch 2 days later.)

Case No.	Blood sugar.†			Urine sugar.†		
	Fasting level.	45 mins. post cibum.	2 hrs. post cibum.	0-45 mins. post cibum.	45 mins. to 2 hrs. post cibum.	Total, 0-2 hrs. post cibum.
1 . . . . .	-7	-8	-122	+0.8	-7.1	-6.4
2 . . . . .	+69	+86	-38	+8.6	-1.5	+7.1
3 . . . . .	+20	+100	+126	+0.7	+9.2	+9.9
4 . . . . .	+16	+30	-30	+1.9	+2.8	+4.6
5 . . . . .	+26	+64	-26	+0.5	+2.7	+3.3
6 . . . . .	-50	-55	-166	-1.4	-1.8	-3.2
7 . . . . .	+9	-63	-80	-0.4	+1.3	+0.9
8 . . . . .	+32	+32	-10	+0.8	+2.8	+3.7
9 . . . . .	+46	-144	+24	-1.7	+1.2	-0.5
10 . . . . .	+59	+24	-34	+0.3	+0.2	+0.5
Mean difference ( $\bar{x}$ )	+22	+6.6	-35.6	+1.00	+0.99	+1.99
$n'$ . . . . .	10	10	10	10	10	10
$\frac{S}{\sqrt{n'}}$ . . . . .	10.80	23.89	25.14	0.905	0.882	1.512
$t$ . . . . .	2.037	2.076	1.417	1.105	1.118	1.314
$P$ . . . . .	0.076	0.79	0.19	0.30	0.29	0.22

\* The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, 3d ed., London, Oliver and Boyd p. 104, 1930). The principle of the method is first to calculate the mean differences between the results obtained with two different experimental procedures. According to Fisher's method, whether or not the difference is significant, is determined as follows: A certain statistical value  $t$  is calculated from the data with the aid of a formula given below. Then taking into account the number of cases in the series a value  $P$  is derived by consulting tables in Fisher's book.  $P$  represents the frequency with which a value of  $t$  (sic. N.B., points) greater than the one obtained in the study could be found purely as a result of chance alone. The convention is to assume that when  $P$  is less than 0.05 the observed difference is significant.

For example, let us consider the results for the fasting blood sugar level. The mean difference, designated by  $\bar{x}$ , is in this instance +22, the plus sign indicating that the value is higher after the administration of starch. The value of  $t$  is derived as follows:

$$\frac{S^2}{n'} = \frac{1}{n'(n'-1)} \left[ \sum x'^2 - n'\bar{x}^2 \right] = \frac{1}{10 \times 9} \left[ \sum x^2 - 10(22.0)^2 \right] = 116.64$$

$$t = \frac{x\sqrt{n'}}{S} = \frac{22.0}{10.8} = 2.037$$

If now the table in Fisher's book is consulted it is found (when  $n = 9$ , where  $n = n' - 1$ ,  $n'$  being the number of cases in the series, and when  $t = 2.037$ ) by interpolation that  $P = 0.076$ . Hence, by the convention referred to above the difference found is not considered significant. This holds true for all the other columns in Table 1.

† The sign of the difference was taken as positive when the values in the experiment with starch were larger, and as negative when the values with dextrose were larger.

reveal any significant differences in the mean concentrations of the dextrose in the blood at all levels. Also, the quantities of dextrose excreted in the urine are almost identical.

It might be argued that the giving of 100 gm. of dextrose caused a reduction in tolerance so that the blood sugar curve when starch was given was higher than it otherwise would have been. One of us (M. W.)<sup>5</sup> has performed 2 dextrose tolerance tests within a period of 2 days on each of 30 diabetics, using 100 gm. of dextrose as the test dose. Careful study of their tolerance before and after this procedure did not reveal the slightest depreciation of their capacity to utilize carbohydrates.

To answer this objection more directly, another series of cases was studied in which the starch was given first and the dextrose 2 days later. The results in this series (Tables 2 and 2a) strikingly confirm the validity of the conclusions drawn from the previous study. In fact, the mean differences obtained here are even smaller than in the first experiment.

TABLE 2.—CONCENTRATION OF DEXTROSE IN THE BLOOD AND QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 90 GM. OF STARCH AND 100 GM. OF DEXTROSE.

(In this series of cases the starch was given first and the dextrose 2 days later.)

Case No.	Blood sugar (mg. per 100 cc. of blood).						Urine sugar (gm.).	
	Fasting level.		45 minutes post cibum.		2 hours post cibum.		Total, 0 to 2 hours post cibum.	
	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.	Starch.	Dextrose.
1	256	330	424	504	436	525	21.2	16.57
2	304	372	386	480	554	533	33.2	29.4
3	320	400	499	512	546	586	33.0	31.9
4	296	267	432	364	500	410	8.0	8.3
5	298	307	518	439	546	592	10.9	7.8
6	284	251	486	414	570	441	18.7	10.7
7	334	318	498	480	562	546	4.5	12.7
8	267	270	435	440	520	606	18.9	17.1
9	310	263	476	444	...	...	3.9	4.5
10	200	238	308	460	356	534	6.8	12.0
11	244	239	435	416	435	488	17.9	17.3
Means	283.0	295.7	445.2	450.3	502.7	526.1	16.09	16.57
Difference between means	12.72		5.09		23.4		0.48	

A second possible objection is that in the first series the concentration of dextrose in the blood, though lower at the "fasting level," was higher at the "2-hour level" when dextrose was given. Hence, when the rise in the concentration of dextrose in the blood is considered it is conceivable that the differences might be significant.

For that reason a special statistical analysis was made of the difference in rise from the "fasting level" to the "2-hour level." In the first series (where dextrose is given first and starch 2 days later), it was found that  $P = 0.021$ , a value less than the conventional limit of significance, which is 0.05. However, the value is not low enough to rule out the possibility of coincidence. This is borne out by a similar analysis of the second series (where starch is given first and dextrose 2 days later), where it was found that  $P = 0.84$ , a value which indicates that the rises in concentration of dextrose in the blood were practically identical.

TABLE 2a.—DIFFERENCES IN THE CONCENTRATION OF DEXTROSE IN THE BLOOD AND THE QUANTITY OF DEXTROSE IN THE URINE AFTER THE INGESTION OF 90 GM. OF STARCH AND 100 GM. OF DEXTROSE.  
(Where starch is ingested first and dextrose 2 days later.)

Case No.	Blood sugar.*			Urine sugar.*
	Fasting level.	45 minutes post cibum.	2 hours post cibum.	Total, 0 to 2 hours post cibum.
1 . . . . .	-74	-80	-89	-9.4
2 . . . . .	-68	-94	+21	+3.8
3 . . . . .	-80	-13	-40	+1.1
4 . . . . .	+31	+68	+90	+0.3
5 . . . . .	-9	+79	-46	+3.1
6 . . . . .	+33	+72	+129	+8.0
7 . . . . .	+16	+18	+16	-8.2
8 . . . . .	-3	-5	-86	+1.8
9 . . . . .	+47	+32	....	-0.6
10 . . . . .	-38	-152	-176	-5.2
11 . . . . .	+5	+19	-53	+0.6
Mean difference $\bar{x}$	-12.72	-5.09	-23.4	-0.48
$n'$ . . . . .	11	11	10	11
$\frac{s}{\sqrt{n'}}$ . . . . .	13.75	22.56	28.44	1.57
$t$ . . . . .	0.926	0.224	0.823	0.306
$P$ . . . . .	0.38	0.83	0.43	0.77

\* The sign of the difference was taken as positive when the values in the experiment with starch were larger, and as negative when the values with dextrose were larger.

**Comments.** As stated above, it is the contention of Allen, which is accepted by Joslin,<sup>6</sup> that dextrose brings on glycosuria and diabetes more actively than starch and that the sudden dextrose flood when dextrose is ingested is more injurious to the pancreatic function than the more gradual and prolonged labor imposed by starch. The findings made by us offer direct proof that such is not the case. *The glycemia and glycosuria after the ingestion of dextrose and of an equivalent amount of starch by diabetics are not significantly different.* Dextrose, therefore, is no more injurious to the diabetic than starch.

**Conclusions.\*** 1. In patients suffering from diabetes mellitus, the glycemia and glycosuria after the ingestion of dextrose and of an equivalent amount of starch do not differ significantly.

2. It may be then concluded that from this point of view dextrose is no more harmful to the diabetic than starch.

We are indebted to Dr. Alexander S. Wiener for statistical analysis of the data.

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\* It is of course obvious that administration of less excessive amounts of dextrose and starch might bring out differences, not apparent here, which would negate the conclusions drawn in this paper.—THE EDITORS.

## DERMATITIS GANGRENOSA.

### A COMPLICATION OF DIABETES MELLITUS.

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GANGRENE in diabetes is ordinarily confined to the lower extremities and is of a progressive nature. Usually it is associated with marked degenerative changes in the peripheral vascular system with obliteration of the blood supply to the involved part. Superficial lesions of the skin without evidence of arteriosclerosis, trauma or infection are rare. In the case reported here there was complete destruction of the superficial and subcutaneous layers of the skin with necrosis and gangrene without any evidence of peripheral atherosclerosis. To this the term "Dermatitis Gangrenosa" has been applied.

**Case Report.** A white female, aged 40, a known diabetic for 3 years, was admitted to the Vanderbilt University Hospital October 8, 1931, after being unconscious for 14 hours following the ingestion of a heavy carbohydrate meal. Except for the typical diabetic coma the examination was essentially negative. The blood sugar was 570 mg., the urine showed 30% glucose and contained acetone and diacetic acid. The usual treatment for diabetic coma was given and within 6 hours she regained consciousness. The following day she was still somewhat drowsy, the urine showed 2% glucose and no acetone bodies. Physical examination revealed over the right kidney area posteriorly a huge bleb, surrounded by an area of edema, filled with a yellowish watery material. There were similar lesions on the posterior surface of both legs. None of these was painful. The distribution of the blebs over the lower extremities, seemed to be only over

those areas where pressure had been made at points where the legs had been crossed. Several theories of the cause of these blebs were considered. First, an allergic reaction to insulin; second, trophic changes as a complication of the diabetes mellitus; and third, a vascular disturbance of an obliterating type with the lesions appearing at pressure points.

The lesions became more widespread with a scattered distribution over the back and the posterior surface of the thighs and legs. The first bleb ruptured and new ones formed. Beef insulin was substituted for pork insulin and calcium chlorid was given but the blebs continued to appear. On October 11, 40 hours after the onset of these lesions it was noticed that superficial ulcers formed at the site of the blebs and that there was a necrosis of the skin and some ecchymosis around the necrotic areas. On the back of both thighs, on the back of the right calf and on the inner side of the left calf particularly over the area where the legs crossed each other there appeared sharply circumscribed superficial areas of tissue destruction

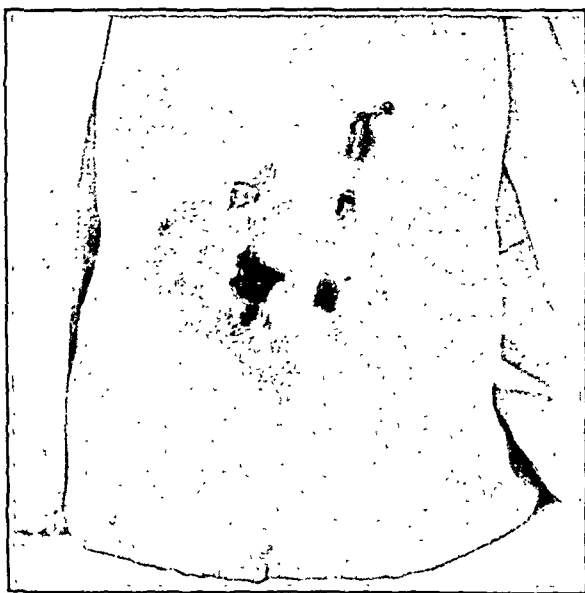


FIG. 1.—The lesions of the skin showing the blebs, the superficial ulcers and necrosis of the skin.

which over most of these areas had gone on to gangrene. They were sharply circumscribed. The gangrenous area was sunken and there was a small zone of erythema around each one (Fig. 1). Over the back there was a series of similar lesions. There was considerable induration around the lesions. The dorsalis pedis arteries were palpable but the patient complained of numbness, tingling and tenderness over both feet. There was little evidence of peripheral vascular disease as far as the larger arteries were concerned. Cultures of the fluid in the blebs repeatedly showed a heavy growth of *Staphylococcus aureus*; probably due to secondary infection.

After the first 10 days, although new blebs continued to appear, an occasional one would be found on the legs and back. These ruptured and left the gangrenous ulcers described above. At the end of 4 weeks the ulcers began to improve, the change was characterized by thick, painless keratinous crusts which were followed by scaling and healing. The skin lesions were treated with dry heat in the form of baking continuously applied to

the exposed surface at a temperature as high as the patient could tolerate. No dressings, ointments or solutions were used. On December 23, when she left the hospital, the lesions on the back had scaled off leaving a purplish discoloration. The ulcers on the legs, although considerably smaller, were still present and covered by hard keratinous scales. (Fig. 2.) Although the lesions were painless she complained of cramp-like pains in the extremities.

*Course in the Hospital.* About 10 days after admission to the hospital she was awakened at 3 A.M. with a sharp pain in the left chest associated with cough, and expectoration of yellowish sputum. This was associated with generalized aching and a febrile rise to  $103^{\circ}$  F. There were no physical signs at first, later examination of the lungs revealed the presence of a slightly impaired percussion note with slightly harsh and high pitched breath sounds and numerous râles persisting after cough, over an area between the fourth and sixth dorsal spine just at the border of the left scapula. The amount of sputum increased, had a sweetish foul odor and varied from 4 to 6 ounces daily. Roentgenograms of the chest showed the

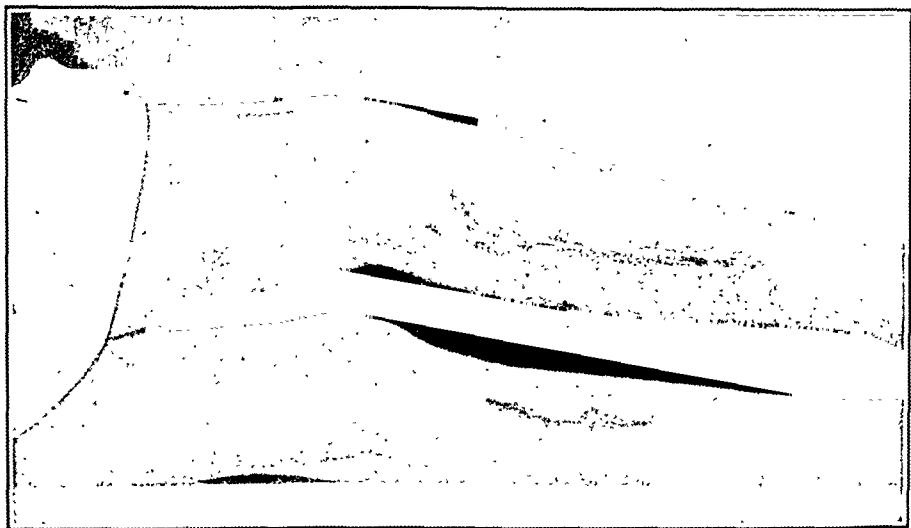


FIG. 2.—Three months later, showing healing and scaling with little scar formation.

presence of a mass in the region of the left hilus interpreted as lung abscess. She was placed on postural drainage and after 1 month roentgenograms showed definite healing. A roentgenogram taken March 2, showed complete healing of the abscess, and there has been no cough, expectoration or fever since then.

On admission the patient had a temperature of  $102^{\circ}$  F. The fever was intermittent in character with an afternoon rise to  $102^{\circ}$  and  $103^{\circ}$ , and a fall to normal during the night and morning. From October 22 to November 20, 1931, the temperature remained elevated and associated with this rise there were marked prostration and cramp-like pains in the extremities but no pain or tenderness over the ulcers. After November 9, the temperature fluctuated between  $99.5^{\circ}$  and  $100^{\circ}$  F. and each febrile rise was associated with the expectoration of large quantities of mucopurulent sputum. The sputum gradually diminished in amount and by December 23, she was raising less than 1 ounce daily. A total of 8 sputum examinations were negative for tubercle bacilli. Blood cultures and agglutination tests were reported negative. There was a slight anemia present, hemoglobin 10 gm.;

red blood cells 3,600,000; white blood cells 10,500 per c.mm. There was never any marked leukocytosis.

The diabetes was easily controlled. The diet on discharge contained 2500 calories, including 55 gm. of protein, 210 of fat and 100 of carbohydrate with 56 units of insulin daily.

By December 23, after 102 days in the hospital, the patient was discharged. Her condition was improved but she was far from cured. The lesions on the back had scaled off and left a purplish brownish pigmentation. She continued to use the hot bakes at home, weighed her diet carefully, and took 56 units of insulin daily. By January 3, the temperature came down to normal and remained there. She complained vigorously of cramp-like pains in the extremities, but not over the site of the lesions. On January 15 the pain was less and she tried walking. It was noticed that after lowering her feet a purplish discoloration developed at the site of the lesions. The legs were elevated for a few days and another attempt was made to exercise them, this time there was no discoloration and walking was encouraged, until she could walk about the house fairly well without much pain. She did, however, notice that on standing for any length of time a swelling would appear around both ankles. The cramp-like pains in the right leg entirely disappeared but she still complained of some prickling and darting pains in the left leg. Her general condition appeared good, the fasting blood sugar after her discharge from the hospital varied from 90 to 130 mg. per 100 cc. of blood.

**Discussion.**—Grangrenous lesions of the skin may be classified in three groups, (1) those due to circulatory disturbance, such as occur in Raynaud's disease and diabetes mellitus, (2) those that occur as trophic changes and, (3) those due to infections and caused by specific organisms. The last type mentioned is that which occasionally occurs in children with the acute exanthemata and is characterized by superficial necrosis. It is also found associated with certain acute inflammatory processes, usually abscesses in which drains have been placed.

The onset of dermatitis gangrenosa is marked by fever, perhaps a chill and prostration. The lesion may first be inflamed or first make its appearance as a large bleb surrounded by an area of edema. The subsequent ulcer extends down to the subcutaneous tissue, and when the overlying skin disappears granulations with shaggy fragments of slough are found. Bloodvessels are greatly dilated, filled with broken down pus cells and red cells. The margin of the gangrene is covered with a fibrinous exudate filled with neutrophils. The base of the ulcer is necrotic and covered with a seropurulent exudate. There is a narrow light red areola of hyperemia extending around the periphery. There may be lymphangitis and enlargement of the regional lymph nodes. Healing is characterized by the formation of a crust followed by scaling and healing.

There is no satisfactory explanation for the development of this form of dermatitis but careful studies have recently appeared concerning a bacterial etiology. Although no specific factor has been found, Brewer and Meleney<sup>1</sup> have been able to produce gangrenous ulcers by inoculation experiments in animals. In their investigation, the non-hemolytic streptococcus, the hemolytic staphylo-



coccus, and a diphtheroid organism were found. When the first two were inoculated separately in animals very little reaction occurred. When they were injected together gangrene was produced. From these results Brewer and Meleney<sup>1</sup> concluded "that a symbiotic function, or combination of functions of these two organisms may be necessary for the production of gangrenous ulcers." Besides this work numerous instances of such lesions have been reported in the literature. It is interesting to note that most of the cases have followed an appendectomy for appendiceal abscess. Cullen,<sup>2</sup> Brewer and Meleney,<sup>1</sup> and Shipley<sup>3</sup> report such cases. Lynn<sup>4</sup> reviewed the literature and reports 29 cases of postoperative gangrenous ulcer of the abdominal wall. Of these 15 occurred in males and 14 in females, and all followed appendicular abscess or peritonitis. However, Gatewood and Baldrige<sup>5</sup> and Meleney<sup>6</sup> have reported gangrenous ulcers following the injection of scarlet fever antitoxin. Warfield<sup>7</sup> reports a case in a patient with alcoholic neuritis and obesity. None of these ulcers have extended any deeper than the muscular aponeurosis and in no instance has there been any history of syphilis or diabetes mellitus.

Several explanations may be offered for the development of "dermatitis gangrenosa" in this case. One, a vascular disturbance of an obliterating type with lesions occurring at pressure points in a patient with a slow circulation and low blood pressure such as occurs in diabetic coma. The other explanations, also speculative, involve such factors as an extensive capillary bed, slow circulation, hyperglycemia, and bacterial invasion of the skin.

Treatment has been under discussion, and no agreement seems to have been reached. Probststein and Seelig<sup>8</sup> have used blood from immunized donors. Cullen,<sup>2</sup> Shipley,<sup>3</sup> Ballin<sup>9</sup> and Lynn<sup>4</sup> have been able to check the process and prepare the ulcer for skin grafting. Some have used quartz light and foreign protein shock. The fact that this has responded to such a gamut of therapy proves there is no accepted specific treatment. In our case treatment was directed toward the diabetes, and the extremities were kept warm.

**Conclusion.** A case of dermatitis gangrenosa is reported. Gangrene in diabetes is frequent especially where there are marked degenerative changes in the peripheral vascular systems. In such instances, however, gangrene is confined to the lower extremities. Superficial lesions are rare. An explanation for the development of the lesions is outlined.

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## TEMPERATURE DETERMINATIONS IN THE FEMALE PELVIS DURING DIATHERMY.

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THE markedly divergent opinions as to the therapeutic efficacy of diathermy in the treatment of pelvic inflammatory disease may be due to variations in the technique of its application. Obviously, the degree of temperature elevation and its duration bear a direct relationship to the therapeutic result obtained. Thus it is not surprising to note that Scheffey and Schmidt,<sup>1</sup> who produced temperatures between 101.5 to 102° F. as indicated by the thermometer in the vaginal electrode, did not obtain the same results as did Cherry<sup>2</sup> and others, who created temperature elevations between 108 and 110° F. as indicated by the vaginal electrode thermometer.

For the sake of accuracy the evaluation of therapeutic results should be related to the temperature elevations in the various parts of the female pelvis and the duration of these temperatures.

There is no method by means of which one may determine the degree of tissue heating which occurs during a pelvic diathermy treatment other than by direct thermal measurement. The reading of the milliamperemeter is no definite guide, because the heat produced by the passage of the high-frequency current varies with the extent of the area of tissue in contact with the electrode; the shape of the electrode; the character of the tissues traversed by the current; the integrity of the local circulation; the effectiveness of the thermoregulatory mechanism of the patient as well as the duration of current flow. The only way, therefore, to know the temperatures obtained during a treatment is by means of actual measurement. We have made such temperature determinations in order to guide us in the development of a technique which would produce the maximum amount of pelvic heating.

The heating effect of diathermy upon the structures of the female pelvis has been noted by several observers. These temperature determinations were made by means of a thermometer inserted into a vaginal electrode.<sup>3</sup> Because it was obvious that a thermometer so inserted measured the temperature of the metal composing

the electrode and not that of the tissues in contact with it, the channel containing the thermometer was extended to the surface so that the tip of the thermometer bulb was brought into contact with the vaginal mucosa.<sup>2</sup> In the effort to determine more accurately the temperatures developed in the treated tissues it was urged that thermometers be placed in the tissues and in no way incorporated into the electrode.<sup>4</sup> The temperatures registered by these thermometers rose to 110° F. and after a few minutes the temperature would drop 1 to 2°. To reestablish an original temperature level it was necessary to increase the current.<sup>5</sup>

Observations have been made of the heat produced in the urinary bladder by means of diathermy. It has been shown that the rate of heating depends upon the concentration of the solution contained within the bladder.<sup>6</sup>

Diathermy produces an increased urinary secretion.<sup>7, 8, 9</sup> This increase has been explained as due to a dilatation of the bloodvessels of the kidney.

The application of diathermy to the pelvis causes an elevation of general body temperature.<sup>3, 4, 10</sup>

It has been shown that the use of "trans-pelvic diathermy" administered by means of plate electrodes placed externally (anterior posteriorly) does not cause any appreciable heating of the pelvic organs.<sup>4, 6, 10, 16</sup> On the other hand other observers have reported increases of rectal temperature as high as 3.6° F. by means of this technique.<sup>17, 18</sup>

**Method.** We have studied temperature changes produced by intrapelvic diathermy. The pulse rate, mouth temperature and the temperature of the voided urine were first determined. The patient was then placed upon the table and draped as for the usual gynecological treatment. A flexible metal belt, which we use as our dispersive electrode, was placed about her waist and connected to one terminal of the d'Arsonval winding of the diathermy machine. Thermometers were inserted as desired, into urethra, bladder, cervix or rectum for the measurement of the local temperatures during treatment. A lubricated vaginal electrode was inserted so that its concavity faced anteriorly and its upper end passed beneath the cervix into the posterior vaginal fornix. The vaginal electrode was connected with the other terminal of the d'Arsonval winding. This electrode (developed by Dr. Derow) is made in three sizes. The largest size compatible with the patient's comfort was used. A clamp support held the electrode and the thermometers in the various orifices.

We used clinical thermometers to measure the temperature of the urine directly after the patient had voided into a paper cup. We determined that the urinary temperatures obtained by this method were about one degree lower than their true values.

To determine the temperatures developed within the tissue of the cervix we employed a thermocouple made of chromel-copal wires inserted through capillary glass tubes placed within a hypodermic needle. With the coöperation of our physicist—Mr. Myron Schwarzschild—we made certain that the thermocouple readings accurately measured the temperatures of the treated tissues.<sup>19</sup>

*Results.* The readings of the vaginal electrode thermometer will here be designated as vaginal temperatures. If the strength of the diathermic current is rapidly increased, to reach the maximal milliamperage within 3 or 4 minutes, the vaginal temperature rises rapidly. When 2000 to 2500 ma. were applied in this manner, in the course of 34 treatments (Table 1), the maximal vaginal temperature, averaging  $108.4^{\circ}\text{F.}$ , was usually reached in 10 minutes.

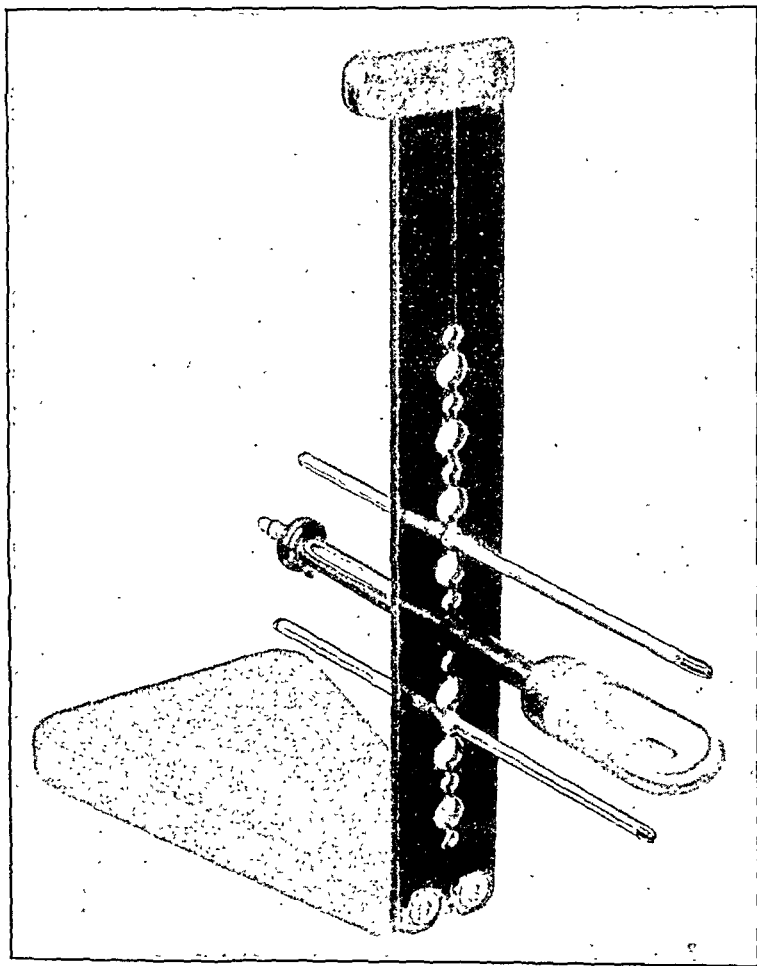


FIG. 1.—Clamp support for electrode and thermometers.

Although the milliamperage remained constant, a drop in temperature occurred averaging  $2\frac{1}{2}^{\circ}$ , during the ensuing 15 minutes. This was followed by a very gradual, slight elevation amounting to about  $\frac{1}{2}$  of  $1^{\circ}$  by the end of the 45-minute treatment.

If we increased the milliamperage gradually, at a rate of 200 ma. each minute, until the maximum of 2000 to 2500 ma. was attained, there was a more gradual and somewhat greater elevation of the

vaginal temperature. As shown in Table 2, during 21 treatments administered in this manner, the maximal vaginal temperature, averaging  $109.8^{\circ}$ , was reached in 16 minutes. This was followed by a drop of  $3.3^{\circ}$  during the succeeding 14 minutes. The vaginal temperature thereafter averaged but a  $\frac{1}{2}^{\circ}$  higher than during the treatments in which the current had been rapidly increased.

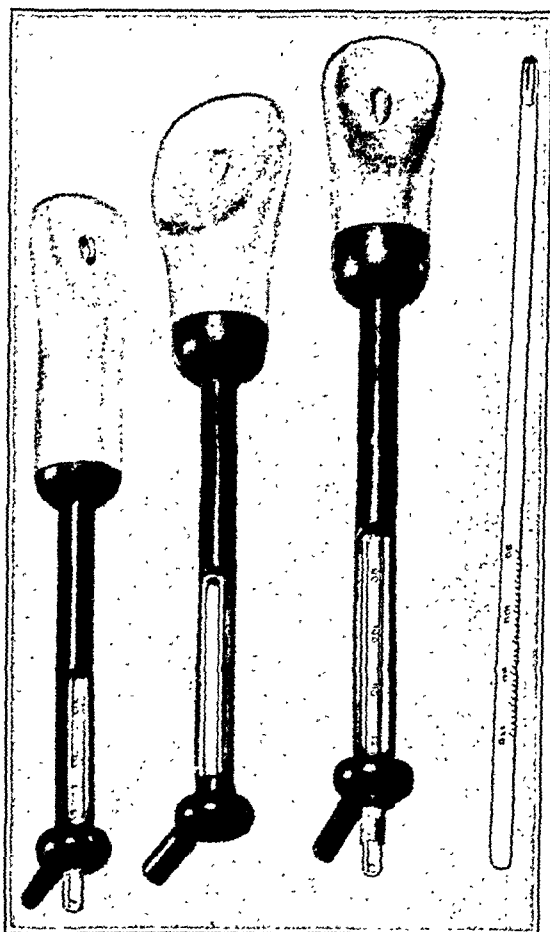


Fig. 2.—Derow vaginal electrode, three sizes.

The addition of more current just before the usual time of the drop in vaginal temperature, occasionally prevented and usually diminished this drop. After much experimentation, the best sustained vaginal temperature was found to be achieved by the following technique: Depending upon the bulk of the patient and the size of the vaginal electrode, the pelvic diathermy treatment was started with 1200 to 1500 ma. Ten minutes after the beginning of treatment, the current was increased another 500 ma., and this

was repeated 5 minutes later. Further increases were at 5-minute intervals, if necessary to maintain the temperature level. It was rarely necessary to exceed 3000 ma.

TABLE 1.—VAGINAL ELECTRODE TEMPERATURES DURING PELVIC DIATHERMY TREATMENTS.

	No. of treat- ments.	Maxi- mal temp.	When reached, min.	Drop to:	When reached, min.	Temp. end of treat- ment.
2000 to 2500 ma. applied in first 3 min.	34	108.4	10	105.9	15	106.4
200 ma. every min. for 10 to 12 min.	21	109.8	16	106.5	14	106.9
to 2000 or 2500 ma. . . . .	255	108.8	19	..	...	107.5
All cases recorded, various techniques						

We have recorded the vaginal temperatures during 255 pelvic diathermy treatments administered to 40 patients. The average maximal temperature was 108.8° F. attained 19 minutes after the beginning of treatment. At the end of treatment, usually after about 45 minutes, the vaginal temperature averaged 107.5°. The highest vaginal temperature registered during any treatment was 112.5° F.

Throughout each treatment simultaneous observations were made every 5 minutes of the temperatures registered by the vaginal electrode thermometer, and by thermometers placed in one or more adjacent cavities.

*Rectal Temperatures.* Rectal temperatures were measured by means of a long mercury thermometer inserted a measured distance into the rectum, and held in place by the clamp support.

The highest rectal temperatures were recorded at a distance between 3 and 5 inches from the anal orifice (Table 2). Below 3 inches and above 5 inches the rectal temperatures were lower. With two thermometers registering simultaneously at varying distances within the rectum, temperature differences were similar to those shown in the table.

TABLE 2.—RECTAL TEMPERATURES AT VARYING DEPTHS DURING PELVIC DIATHERMY TREATMENT.

Penetration of thermometer, inches.	No. of treatments.	Maximal temp.	When reached, min.	Temperature end of treatment.
1½ . . . . .	5	105.0	39	104.9
2 . . . . .	10	106.3	32	105.8
2½ . . . . .	7	105.7	19	104.7
3 . . . . .	35	107.1	22	106.2
3½ . . . . .	17	107.3	21½	105.9
4 . . . . .	54	107.7	22	106.5
4½ . . . . .	3	108.7	27	106.7
5 . . . . .	7	107.1	15	106.1
6 . . . . .	3	103.9	25	103.9
Average rectal (all depths) . . . . .	191	107.3	20	106.1
Average vaginal temperatures . . . . .	255	108.8	19	107.5

In Table 2, it is seen that the average rectal temperature determined during 191 treatments, closely followed the average vaginal temperature, attaining its maximum at almost the same time, but remaining a degree and a half lower throughout.

*Urethral and Bladder Temperatures.* The temperatures registered within the bladder increased with the depth to which the thermometer was inserted. Three and 4 inches from the urethral meatus, the average maximal bladder temperatures were within a half degree of the average maximal vaginal temperatures, but were attained 6 to 13 minutes later. These deep bladder temperatures were better sustained than were the vaginal or rectal temperatures. At the end of treatment, the average bladder temperature had dropped but three-tenths of a degree from its maximum and was actually higher than the average terminal vaginal temperature.

The urethral temperatures averaged about 3 degrees lower than the deep bladder temperatures.

TABLE 3.—URETHRAL AND BLADDER TEMPERATURES DURING PELVIC DIATHERMY TREATMENTS. WITH THERMOMETER CONTINUOUSLY AT INDICATED DEPTHS FROM MEATUS.

Penetration of thermometer, inches.	No. of treatments.	Maximal temperature.	When reached, min.	Temperature end of treatment.
1 . . . . .	9	105.6	23	105.0
1½ . . . . .	98	105.8	26	105.3
2 . . . . .	20	106.5	29	106.2
3 . . . . .	12	108.2	32	107.9
4 . . . . .	4	108.7	25	108.4
Average vaginal temperatures	255	108.8	19	107.5

*Urine Temperatures.* Using the paper cup and clinical thermometer method previously described, the temperature of the urine before treatment averaged 98.4° F. on 271 occasions.

The temperature of the urine voided within a few minutes after the termination of treatment averaged 105° F. on 116 occasions. Since the determinations by this method proved to be about a degree lower than their true values, the temperature of these urines really averaged about 106° F.

In a few cases the urine was drained directly into a thermos bottle by means of a catheter, the catheter and thermos bottle having been previously heated to 100° F. Urine temperatures of 107° F. and over, were several times recorded by this technique.

*Changes in Urine Concentration.* Following about two-thirds of the treatments there occurred a diminution in the specific gravity of the urine varying between 0.002 and 0.014—averaging 0.005.

*Mercury Thermometer Measurements of Cervical Canal Temperatures.* Temperatures within the cervical canal were recorded simultaneously with the vaginal electrode temperatures during 8 pelvic diathermy treatments. We made certain by verifying its position at the termination of the treatment, that the entire bulb of the thermometer lay within the cervical canal. The cervical

temperatures closely followed the vaginal, averaging about 1 degree lower.

*Thermocouple Measurement of Cervical Tissue Temperatures.* In order to observe how the temperatures recorded by means of a thermocouple compared with the readings of a mercury thermometer, we inserted a thermocouple needle together with the bulb of a mercury thermometer into a cervical canal. The electrode was then introduced into the vagina, its end passing under the cervix without disturbing the cervical thermometers. The preliminary readings of the thermocouple and the thermometer in the cervix were almost identical (Table 4), while the vaginal electrode had not quite warmed up to body temperature. When the diathermy current was turned on, the thermocouple registered the elevation in temperature a little more rapidly than the cervical thermometer. Nineteen minutes from the beginning of the treatment the temperature recorded by the thermocouple, cervical thermometer and vaginal electrode thermometer simultaneously reached their peaks, with the thermocouple registering a temperature  $0.9^{\circ}$  F. higher than the mercury thermometer beside it. The subsequent drop in thermocouple temperature was also more rapid as was the further drop when the diathermy current was turned off. These differences are explained by the greater sensitiveness of the thermocouple. In this case the temperatures registered by the vaginal electrode thermometer were exceeded by the cervical canal temperatures.

TABLE 4.—THERMOCOUPLE AND MERCURY THERMOMETER SIDE BY SIDE IN CERVICAL CANAL.

Time.	Cervical temperature.		Vaginal electrode temperature.
	Thermocouple.	Mercury thermometer.	
3:17 . . . . .	98.5	98.6	96.6
3:18—2000 ma. on			
3:20 . . . . .	101.8	101.0	100.0
3:22 . . . . .	103.0	102.5	102.0
3:24 . . . . .	104.0	104.0	102.8
3:26 . . . . .	104.4	104.2	103.4
3:28 . . . . .	106.6	106.0	105.4
3:30 . . . . .	108.1	107.5	106.5
3:35 . . . . .	108.9	108.0	107.0
3:37 . . . . .	107.6	107.8	106.6
3:39 . . . . .	106.3	106.5	106.0
Machine off			
3:40 . . . . .	104.1	105.0	104.0
3:44 . . . . .	100.0	100.8	100.0

The thermocouple needle was inserted into the cervical tissue at different places. During the treatment, simultaneous observations were made at 2-minute intervals, by one worker with the thermocouple and by another reading the thermometers in the vaginal electrode and cervical canal. Thermocouple temperature usually was within 1 or  $1\frac{1}{2}^{\circ}$  F. of the vaginal temperature.



In one instance we observed that the cervical tissue temperature rose to only 105° F. when the vaginal electrode thermometer read 109.5° F. In a few observations the temperature of the cervical tissue (as determined by thermocouple) was from 2 to 3° F. lower than that recorded by the vaginal thermometer.

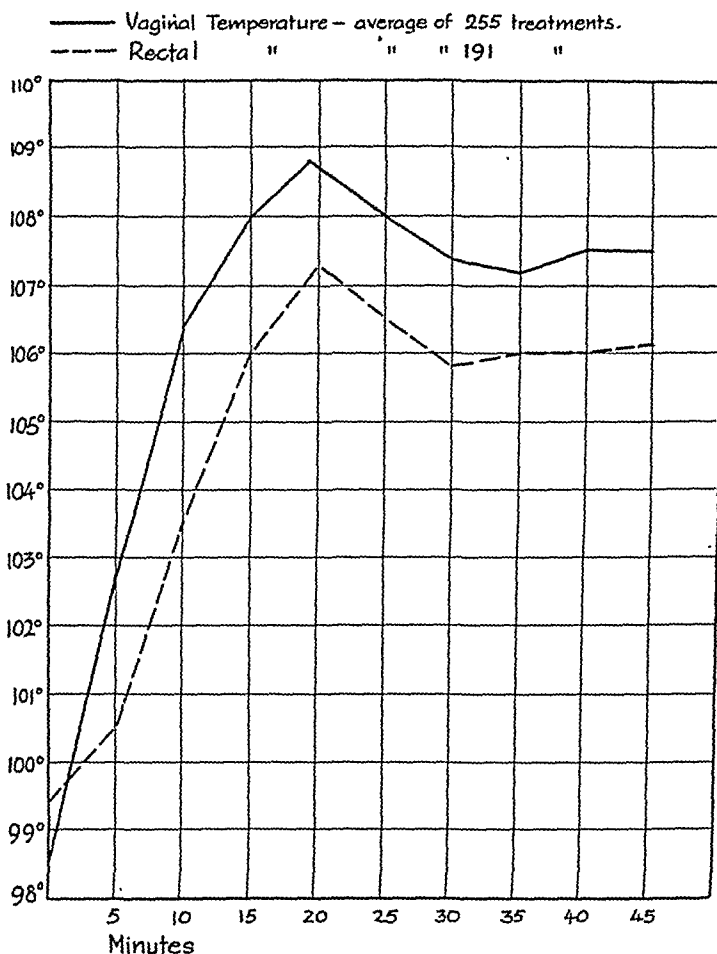


CHART I.—Average vaginal and rectal temperatures during diathermy.

*Mouth Temperature Changes Following Pelvic Diathermy Treatments.* An elevation of mouth temperature occurred following 215 (81%) of 264 pelvic diathermy treatments administered to 41 patients. This elevation varied between 0.1 and 2.4° F., the average being 0.7° F. A drop in mouth temperature followed 24 of the treatments. This drop varied between 0.2 and 1°, averaging 0.35°. Following the remaining 25 treatments, no change of mouth temperature was observed.

*Pulse Changes Following Pelvic Diathermy Treatments.* Of 267 treatments, 214 (80%) were followed by elevation of the pulse

rate, varying between 2 and 34 beats per minute and averaging 12 beats per minute.

In most instances the pulse elevation was accompanied by an elevation of mouth temperature. Occasionally the pulse was accelerated without a change of mouth temperature or even with a slight drop of mouth temperature. In a few cases there was an elevation of mouth temperature while the pulse was unchanged or had dropped a few beats per minute.

*The Pelvic Heating by External Plate Electrodes.* The highest internal temperatures which we have observed in any case during transpelvic diathermy, using large anterior and posterior plates, were: rectal 103.2° F., vaginal 102.2° F., bladder 101.9° F. The thermometers had been inserted at a depth of 3 inches into each of the orifices. A posterior plate 15 by 9 inches was used, and an anterior plate of 9 by 9½ inches. The treatment lasted 45 minutes and the maximal current was 2000 ma. The patient was uncomfortable during the latter part of the treatment because of excessive heating under the plates. An elevation of 1.2° F. in mouth temperature followed this treatment. During 8 other treatments with large anterior and posterior plate electrodes, the milliamperage averaged 1500 ma. The maximal rectal temperatures varied between 99.6 and 101°, the vaginal between 99.5 and 100.5°, the bladder between 99.8 and 100.5°. The cervical temperature never exceeded 99.9°. The temperatures mentioned were the maximal during the individual treatments. They were attained toward the end of treatment. The temperature of the urine voided after these treatments showed no appreciable elevation.

The region most heated by diathermy when applied with external plate electrodes appears to be the skin under the pubic margin of the abdominal plate. On one occasion a temperature of 109° F. was registered by a thermometer with its bulb under the abdominal plate at this point, 11 minutes after the beginning of treatment. 1500 ma. were used. The temperature under the electrode dropped during the ensuing 23 minutes and at the end of the 45-minute treatment was 105° F. It is interesting to observe that the temperature under the abdominal plate electrode when plotted on a chart shows the same characteristic drop as does the temperature curve obtained when using the active vaginal electrode technique.

*Pelvic Diathermy with Rectal and Belt Electrodes.* The pelvic organs may be effectively heated by diathermy when using a large rectal electrode in place of the vaginal electrode. The rectal electrode should have a large surface area so that a large amount of current may be applied without injury. A cylindrical electrode 4 inches long and ¾ to 1 inch in diameter, with a rounded end, is convenient for use in adults. For children we use a cylindrical rectal electrode 3 inches long. With the belt electrode about the waist and the large rectal electrode, 2000 to 2200 ma. are well

tolerated, and produce a temperature in the vagina of 106 to 108° F. After such treatment the bladder urine is likewise heated. We use the rectal electrode infrequently, chiefly for the treatment of virgins, because patients find its insertion somewhat disagreeable.

*Discussion of Results.* The average values reported are a reasonable true index of pelvic heating, but variations were encountered in individual cases. This is inevitable because the heating of the tissues by the current depends not only on the strength and duration of the current flow and the areas of application of the electrodes, but also upon the electrical resistance of the tissues. In addition there are variations due to differences in physiologic and pathologic conditions.

The vaginal electrode constructed of metal, is an excellent conductor of electricity and is not itself heated by the passage of the current. As it is also an excellent conductor of heat, it more or less rapidly assumes the temperature of the tissues with which it is in contact. When an electrode is equipped with a thermometer, the bulb of which is enclosed within it, the temperature recorded is the resultant of the temperatures of all points in contact with the electrode.

In the electrode which we used, the thermometer lies in a metal channel extending through the shaft into the active part of the electrode. About two-thirds of the surface of the thermometer bulb is in contact with the metal channel and the remainder is exposed for contact with the vaginal mucosa. For experimental purposes one of these electrodes was made with an additional channel for insertion of a second thermometer, inside the electrode. Simultaneous readings were made of the two thermometers, one entirely enclosed within the metal, the other partially in contact with the mucosa, throughout the diathermy treatment. It was found that the latter thermometer (the arrangement we use in practice) showed a slightly more rapid rise in temperature, was at first  $\frac{1}{2}$  to 1° higher and reached its maximum 4 or 5 minutes before the thermometer within the electrode. During the latter part of the treatment the two thermometers agreed fairly closely. We consider the thermometer in the vaginal electrode a valuable index of pelvic heating and a reliable guide during treatment.

By means of the paper cup-clinical thermometer method previously described, we measured the temperature of the urine before and after 35 Elliot treatments<sup>20</sup> administered at our clinic. The bladder temperatures attained during these treatments, as measured by a mercury thermometer introduced several inches beyond the urethral meatus, varied between 103 and 105.8° F. The urines voided after treatment, however, averaged but 99.4° F. The highest urine temperature was 101° F. Although the bladder wall had been heated through by conduction, the urine was evidently heated very little. During pelvic diathermy treatments the heating of the

bladder wall averaged but 2 or 3° higher than during the Elliot treatment, yet the temperatures of the bladder urine averaged 5½° higher. This could be explained by a direct heating of the urine itself, by the diathermy current.

The heating of the fluid in the bladder by the current and the well-sustained bladder temperatures suggest the likelihood that other fluid collections adjacent to the vagina, such as occur in the course of pelvic inflammation, may be heated similarly.

The relatively lower urethral temperatures reported by us, averaging almost 3° below the vaginal temperatures, demonstrate that the electrodes used were not adapted for maximal urethral heating. The electrodes were primarily intended for the treatment of pelvic inflammation and in a deep vagina, lay well above the urethra. Longer vaginal electrodes have recently been constructed.

Our intracervical temperature determinations were made by means of thermometers inserted within the cervical canal. We followed this procedure only in non-infected cases and under aseptic precautions. Otherwise, we would consider this procedure a potentially dangerous one. To quote Curtis, "There is distinct danger of low grade salpingitis from repeated instrumentation of the infected cervix."<sup>21</sup> We, therefore, do not consider it advisable routinely to insert a thermometer into the cervical canal and to keep it there throughout each pelvic diathermy treatment as suggested by Royston, Ewerhardt, Roblee and Zener.<sup>4</sup>

In considering the elevation of mouth temperature following 80% of our diathermy treatments, it should be remembered that the patients were draped with a sheet, just as for any other gynecologic treatment. No extra covering was used for the purpose of lessening heat dissipation. The fact that mouth temperature elevation did occur shows that heat was introduced into the bodies of these patients faster than they were able to dissipate it.

**Conclusions.** By means of a vaginal electrode equipped with a thermometer, the vaginal temperature was observed during 255 pelvic diathermy treatments.

A technique is described by means of which the vaginal temperature may be maintained at a high level.

By means of mercury thermometers in cervix, bladder and rectum, the temperatures developed in these parts were found to follow closely the vaginal temperature, averaging but 1 or 1½° F. lower.

The use of a thermocouple needle demonstrated substantial heating of the tissue of the cervix.

The bladder urine was also heated to a high degree.

It has, therefore, been found that with the electrodes and milliamperages used, the reading of the thermometer in the vaginal electrode is a true indication of the temperatures attained in adjacent tissues.

Mouth temperature and pulse were elevated in 80% of the treatments.

The ineffectiveness of "trans-pelvic diathermy" by external plate electrodes as a method of pelvic heating was once more demonstrated.

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### ACUTE PRIMARY DIAPHRAGMITIS (HEDBLÖM'S SYNDROME).

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For some undetermined reason acute primary inflammation of the diaphragm went unrecognized and some neighboring organ received the blame for the trouble. Even in the works of Hippocrates<sup>1</sup> a mere mention is made of the anatomic aspects of the diaphragm. (Hippocrates' term "acute phrenitis," of course, refers to inflammation of the brain, not of the diaphragm.) We mention this point because of the recent popularization of such misnomers as phrenico-exairesis, or phrenicectomy, terms used for operations on the phrenic nerve which intend to paralyze the diaphragm in the treatment of pulmonary tuberculosis.

Obviously, the cacophonous term "acute diaphragmitis" is resorted to because the muscle is known by only one name. It would be

more euphonious as well as serviceable to refer to this entity as "Hedblom's syndrome" in honor of Dr. C. A. Hedblom who has devoted his life to thoracic surgery and died a few minutes after delivering one of his numerous presentations, all of which aided in placing the specialty of thoracic surgery on a popular footing.

This condition first attracted our attention in 1931, when we saw a patient with the following clinical picture:

**Case Reports.** CASE 1.—Mr. P. D., a Greek fruit peddler, aged 38, was caught in the rain, October 11, 1931, and remained wet for 8 hours. By the time he reached home he developed a severe chill, a temperature of 103° F. and an abdominal pain. The pain was generalized at first, but later became localized in the right side of the abdomen. When seen by us, 2 hours after onset of the chill, the patient had painful breathing (ponopnea) and the only comfort he could have was in a sitting position. At this time the lungs showed no evidence of any involvement. There was a definite muscle spasm in the abdomen but generalized to the whole right side. The patient was sent to the Columbus Hospital, where a conservative régime was instituted in view of the absence of vomiting and leukocytosis. A basal pneumonia of the influenzal type was suspected. The patient was given inhalations of oxygen until his breathing became less labored and morphin until the pain subsided. He was kept in a semi-Fowler position because it gave the greatest comfort.

The next day the patient had a friction rub and subcrepitant râles in the right base. By October 14 the symptoms in the abdomen disappeared. He showed some tendency to cough but refrained because of pain it produced. On the next day the temperature came down to normal and remained there until he left the hospital, on October 16, 1931. When discharged he still complained of slight pain in the back of his chest on deep inspiration but the lungs showed no stethoscopic or other evidence of involvement. He was tagged with a diagnosis of influenzal pneumonia, but we were not satisfied with that classification because of the atypical picture of a pneumonia or appendicitis.

The exact etiology of the above syndrome revealed itself to us when we saw a patient who died following a perforated peptic ulcer. At autopsy he revealed a massive inflammation of the diaphragm with the formation of thick fibrinous exudate extending to the pleural side. An analysis of certain similarities of the symptom complex in the 2 cases lead us to assume that the diaphragm was really at fault in the first case. The following is a report of the second patient:

CASE 2.—Mr. G. K., a German salesman, aged 47, enjoyed excellent health with the exception of a right inguinal hernia. No history of previous gastro-intestinal trouble. He developed the hernia 8 years ago by lifting a heavy suitcase. The company surgeon advised a truss which he wore for 8 years. Present illness started on April 3, 1932, with a severe stabbing pain in the abdomen which developed when he attempted to get up from bed. There was nausea but no vomiting, urinary retention or hematuria. When seen 30 minutes later, the patient was in agony. He presented a typical Hippocratic facies with sunken cheeks and eyeballs, beads of cold perspiration on his forehead and temples. The knees were drawn. Even the jarring of the bed aggravated the pain in the abdomen, which was rigid. Respirations were labored and painful. The pulse

from 68 to 74 per minute. There was definite tenderness over the sac of a hernia which would not remain reduced because of the marked straining by the patient. The truss caused severe pain when applied and was therefore removed. The pain did not subside even with morphin, given in 2 doses of  $\frac{1}{4}$  gr. each at an interval of 15 minutes. An examination of the chest showed no pulmonary or cardiac lesions to account for these symptoms. The patient was sent to the Columbus Hospital. There was no doubt that he presented an acute surgical condition of the abdomen, but was in shock, had a hernia which may have been strangulated and also presented signs of an upper right quadrant lesion that required surgical intervention. Of 3 surgeons who saw him, 2 decided against intervention, while the third insisted on a laparotomy, either in the upper abdomen or at the site of the hernia. A perforated ulcer was suspected but a Roentgen ray film revealed no pneumoperitoneum. On admission the white count was 6000 but on the following day it rose to 30,000. The severity of the condition was discussed with the wife, and the advisability of an exploration was discussed with her. As she refused operation, a watchful waiting régime was followed.

The pain in the abdomen persisted and was somewhat relieved by the use of opiates in large doses. The ponopnea persisted. There was no cough and no vomiting. The respirations were entirely costal in type, while the abdominal wall remained entirely rigid and immobile. A chest examination 24 hours after admission revealed mucous râles on both sides anteriorly and in the axillary areas. The facies of agony remained until the patient went into coma, about 5 hours before death, on April 6, 1932. About an hour before death there was persistent frothing from the mouth, indicating an acute edema of the lung.

At *autopsy* (Dr. Nora) the lungs showed acute edema, with no free pleural fluid. The diaphragmatic surface of the right lung as well as the pleural surface of the diaphragm showed a thick gray exudate with fibrinous adhesions between the lung and the diaphragm. The *heart* showed no important gross lesions. The *abdomen* contained some free seropurulent exudate. The serosal vessels of the whole bowel were injected. No gangrene was present. Above the hepatic flexure 500 cc. of thick grayish-yellow fluid were pocketed between the liver and the diaphragm. The peritoneal surface of the diaphragm showed a thick deposit of grayish-yellow bread-and-butter type of exudate. On further investigation a prepyloric perforated ulcer was located on the side of the lesser curvature. The perforation was the size of a dime; the area around it showed no induration. On section, the diaphragm was 3 times the thickness of its mate on the left side. The cecum and the site of the hernia showed no important lesions. There were no lesions in the pancreas, thus eliminating our suspicions of a possible hemorrhagic necrosis.

Analysis of this case reveals a silent prepyloric ulcer which on perforating caused a hyperacute diaphragmitis and local peritonitis as evidenced by the ponopnea and the board-like rigidity of the abdominal muscles. The ulcer may have been covered at a previous time by means of protective local peritoneal reaction. The ulcer undoubtedly perforated into this sac, thus preventing a generalized peritonitis. It is obvious why the patient did not have any vomiting since there was a relative absence of a generalized peritonitis. The diaphragm, therefore, received the greatest insult and consequently we noticed clinically an immobilization of the diaphragm as evidenced by costal breathing, ponopnea and painful cough.



FIG. 1.—Case 3. Roentgenogram, taken on August 9, 1934, shows a definite rise of the right diaphragm. There is a slight obliteration of the normal dome of the diaphragm, and also a definite infiltration in the right hilum.



FIG. 2.—Case 3. Roentgenogram, taken on August 14, 1934, shows the hilar shadow cleared up. There is a rise of the diaphragm on the right side. The dome of the diaphragm is still evident.





FIG. 3.—Case 3. Roentgenogram, taken on September 17, 1934. The pulmonary markings show no evidence of acute lesions. The dome of the diaphragm is almost entirely obliterated. The costophrenic angle is now about 90 degrees. There is a definite rise of the right hemidiaphragm.

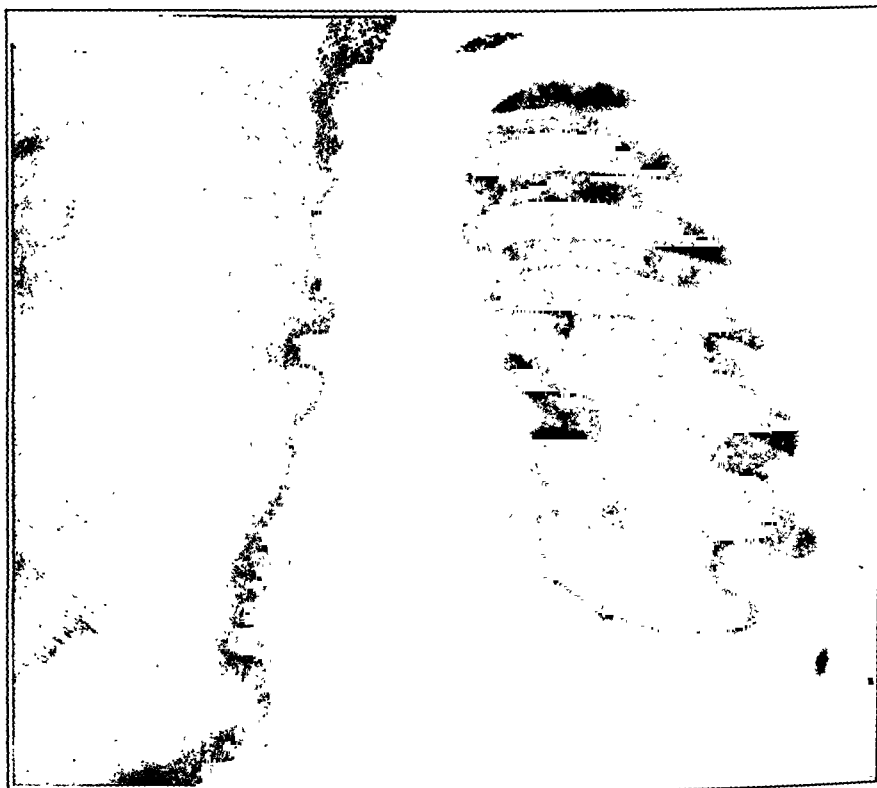


FIG. 4.—Case 3. Roentgenogram, taken on November 17, 1934. The Roentgen ray

The similarity of this syndrome in the 2 patients as evidenced by abdominal pain, painful respiration and immobilization of the diaphragm lead us to suspect that the primary factor in the first case was an acute diaphragmitis. That such a syndrome is possible has been proven to our satisfaction by the third case, in which we have been able to demonstrate roentgenologically an immobilization of the diaphragm and the subsequent evidence of diaphragmatico-pulmonary adhesions.

CASE 3.—Mrs. E. A., a Greek housewife, aged 40, presented herself on July 30, 1934, complaining of headache, nasal discharge and sore throat. On August 9, 1934, she called us to see her at the Garfield Park Hospital, because of pain in the region of the costal margin, at the angle of the scapula and the upper right quadrant of the abdomen. She placed herself under the care of a neighboring physician, (Dr. P. Hatzis), who made a diagnosis of right-sided pneumonia, based on the presence of râles in the chest. When seen by us, she still complained of the characteristic pain in the lower chest and upper abdomen but also had painful breathing. There was little or no cough. On the basis of our previous experience with the other 2 cases we arranged for a fluoroscopic examination which revealed an immobilization of the right leaf of the diaphragm. Roentgen films showed a slight rise of the right hemidiaphragm and a normal dome. There was also some evidence of parahilar infiltration of the lung which was diagnosed by Dr. Wait,\* the roentgenologist, as pneumonia. She made an uneventful recovery. She was seen at our office on several occasions since her discharge from the hospital and a serial study of her diaphragm offers us a distinct proof that this patient suffered from Hedblom's syndrome. The Roentgen ray studies reveal a moderate rise of the diaphragm on the involved side. There is also a gradual obliteration of the normal dome of the hemidiaphragm no doubt due to one of two causes. Either fibrous tissue which may have been deposited is beginning to contract, or else costophrenic adhesions are pulling on the muscle and cause the gradual elimination of the normal dome.

**Discussion.** It may be considered bold of us to attempt the description of a new syndrome. We have hesitated for 2 years, until we felt certain of our ground. We believe that the serial Roentgen ray evidence is conclusive enough to encourage us to publish our observations.

There is no doubt that the syndrome is common and goes unnoticed because an associated picture masks the original entity. We believe that a lot of so-called pleurisies, particularly of the diaphragmatic type, are really those of Hedblom's syndrome. This may be also true of cases of so-called mild appendicitis, or cholecystitis. Certain basal pneumonias probably have their origin in an acute inflammation of the diaphragm.

The intimate relationship of the transversus abdominis with the diaphragm at their points of insertion<sup>2</sup> may explain the muscle spasm and rigidity of the abdominal muscles when the diaphragm is involved.

One may expect to encounter hiccough in such a syndrome.

\* Through the kindness and permission of Dr. Wait the Roentgen pictures are reproduced for record and study.

This obviously is not to be expected, because hiccough in our experience is a phenomenon that involves the esophagus primarily and the pillars of the diaphragm secondarily. It is worthy of note at this point that the diaphragmatic pillars, although in some species an intimate part of the muscle, have a gastro-intestinal function.<sup>3</sup> Since in this syndrome the wing of the diaphragm is involved one may not expect hiccough.

Hedblom's syndrome evidently follows an acute nasopharyngeal inflammation much in the same manner as pneumonia, influenza, or even some cases of acute appendicitis. We are justified, therefore, in assuming that this syndrome is primary. Obviously, it may occur secondarily following lesions in the organs immediately above or below the diaphragm. When primary, it may be masked by more evident associated conditions. The presence of ponopnea should always lead us to suspect this syndrome.

**Summary.** 1. A hitherto undescribed syndrome is presented. It is hoped that it will be recognized as Hedblom's syndrome because it appears to be a distinct condition; the term is more suitable and phonetically more pleasing than acute diaphragmitis and because it honors this pioneer in thoracic surgery.

2. This syndrome is evidenced by painful breathing (ponopnea), painful coughing, an immobilization of the diaphragm as evidenced by the Roentgen ray and costal breathing. There is also abdominal pain involving generally the upper abdominal quadrant. Likewise there may be pain at the costal margin or even at the angle of the scapula.

3. Pathologically the diaphragm undergoes the changes of an acute exudative and proliferative inflammation. We believe that some of the muscle fibers are replaced by scar tissue and thus a flattening or even disappearance of the normal dome of the diaphragm results. The pleural surface may be involved by contiguity and cause diaphragmatico-pulmonary adhesions. The infectious agent causing the syndrome may extend by contiguity to the intrathoracic organs above or the intraabdominal organs below.

4. This report is made in the hope that others will be on the lookout for the syndrome and particularly to avoid unnecessary operations on the abdominal viscera.

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# VITAMIN A CONTENT OF HUMAN LIVER.

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EVANSVILLE, INDIANA.

THE vitamin A content of 15 human livers obtained at autopsy, was determined.

**Method.** The total weight was noted. To each 100 grams of finely ground liver 500 cc. of 5% potassium hydroxid solution were added. After standing 48 hours this mixture was extracted 8 times with ether, and the extract washed 3 times with distilled water, or until the washings were not alkaline to litmus; the water removed by adding anhydrous sodium sulphate. It was then filtered and evaporated under vacuum to dryness. The residue was weighed as unsaponifiable matter. Spectrophotometric determinations on the non-saponifiable material were determined on Hilger's vitameter.

TABLE 1.—VITAMIN A CONTENT OF LIVERS OF 8 "HEALTHY" PERSONS.

Case.	Age.	Cause of death.	Total weight liver (gm.).	Non-saponifiable material in 100 gm.	Total No. I. U. of vitamin A in liver.	No. I. U. vitamin A per gram.	Remarks.
1	36	Pulmonary abscess (Vincent's)	2198	.237	129,682	59	Poor appetite; ill 3 months.
2	68	Heat prostration	2446	4.117	24,680	10	Diet: Low in vit.
3	73	Coronary thrombosis	1642	1.066	128,503	78	Diet: Unknown.
4	52	Accidental, fractured cerv. spine	1470	9.155	1,793,400	1220	Diet: Varied.
5	52	Coronary thrombosis	1860	1.415	169,427	91	Diet: Varied.
6	19	Accidental, ruptured stomach	2082	.539	294,187	141	Diet: Varied.
7	70	Coronary thrombosis	1792	.733	250,880	140	Diet: Unknown.
8	69	Cardiorenal vascular disease	1825	2.234	1,164,350	638	Diet: Unknown.

Cases 1 to 8  
Cases 2 to 8

Average 297  
Average 331

**RESULTS.** In Table 1 are listed 8 cases which averaged 297 I. U. of vitamin A per gram of liver. All of these patients had a sudden lethal exodus except 1 (Case 1), who was ill with a pulmonary abscess (Vincent's) for 3 months. The 7, who were apparently healthy, averaged 331 I. U. of vitamin A per gram of liver. Case 2 lived on a houseboat and had a definitely low vitamin intake. Cases 4 and 6 were well nourished and well developed individuals. Both had

accidental deaths. Case 6 was known to have had a varied diet during his entire lifetime. Cases 4 and 8 evidently stored large quantities of vitamin A in the liver without the addition of any known quantity of vitamin A to their diets.

In Table 2 are listed 5 cases of tuberculosis, 3 of whom had been given additional vitamin A as halibut liver oil,\* and 2 had had a high vitamin diet. Cases 9 to 12 averaged 523 I. U. of vitamin A per gram of liver. Case 13 is not included here because of the excessive administration of vitamin A—4,899,200 I. U. as halibut liver oil over a period of 142 days, 10 months before death. Loss of appetite was the cause for discontinuing the halibut liver oil. A total of 2,509,322 I. U. of vitamin A were found in the liver at death, or 3359 I. U. per gram.

TABLE 2.—VITAMIN A CONTENT OF LIVERS OF 5 CASES OF TUBERCULOSIS.

Case.	Age.	Dosage duration (days).	Total dosage H. L. O (gm.).	Total No. I. U. vitamin A adminis.	Cause of death.	Total weight liver (gm.).	Non-saponifiable material in 100 gm.	Total No. I. U. vitamin A in liver.	No. I. U. vitamin A liver per gram.	Remarks.
9	21	...	...	...	Cerebral embolism and Tb. of hip joint	1291	.808	794,223	615	High vitamin diet
10	28	22	33.0	1,056,000	Pul. Tb., laryn. Tb. and intestinal Tb.	1426	1.905	543,306	381	Vit. A as H. L. O. High vitamin diet
11	18	12	18.0	576,000	Miliary Tb.	1070	.424	779,441	728	Vit. A. as H. L. O. High vitamin diet
12	30				Miliary Tb.	1833	3.853	676,377	369	High vitamin diet
Average									523	
13	57	142	153.1	4,899,200	Chr. Pul. Tb.	747	1.297	2,509,322	3359	Vit. A as H. L. O. High vitamin diet

In Table 3 are listed two children, who averaged 80 I. U. of vitamin A per gram of liver.

TABLE 3.—VITAMIN A CONTENT OF LIVERS OF 2 INFANTS.

Case.	Age.	Cause of death.	Total weight liver (gm.).	Non-saponifiable material in 100 gm.	Total No. I. U. of vitamin A in liver.	No. I. U. of vitamin A per gram.	Remarks.
14	2 yrs.	Miliary Tb.	500	2.244	47,715	95	Diet: Goat's milk.
15	1 mo.	Enlarged thymus	90	.642	5,796	61	Diet: Breast fed.
Average						80	

\* Purchased from Mead Johnson and Company, Evansville, Indiana.

**Discussion.** Wolff<sup>1</sup> and Moore<sup>2</sup> reported on the vitamin A content of human liver by using the antimony trichlorid method. Wolff's cases averaged 250 "Blue units" per gram. Moore reported that the average vitamin A reserve was 235 Blue units per gram. However, this method is not sufficiently accurate in quantitative determinations of vitamin A. The spectrophotometric method employed in this work has been approved by the International Conference on Vitamin Standardization.<sup>3</sup> In this series, 7 cases (Cases 2 to 8 inclusive) in apparently good health ranged from 10 to 1220 I. U. per gram, or an average of 331 I. U. of vitamin A per gram of liver.

**Summary.** 1. Spectrophotometric determinations of vitamin A content of human livers were performed in 15 cases.

2. Seven apparently healthy persons, dying sudden accidental deaths, averaged 331 I. U. of vitamin A per gram of liver. Two children averaged 80 I. U. of vitamin A per gram of liver. Four cases of pulmonary tuberculosis on a high vitamin diet averaged 523 I. U. of vitamin A per gram of liver.

3. The addition of vitamin A as halibut liver oil stores a large quantity of vitamin A in the human liver.

#### REFERENCES.

1. Wolff, L. K.: *Lancet*, 2, 617, 1932.
2. Moore, T.: *Ibid.*, p. 669.
3. Foreign Letters: *J. Am. Med. Assn.*, 103, 5, 353, 1934.

## BOOK REVIEWS AND NOTICES

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THE ADVANCE OF SCIENCE. Edited by WATSON DAVIS, Director, Science Service, Washington. Pp. 400; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1934. Price, \$3.50.

THIS popularizing assemblage by the Director of Science Service (21 of the 32 chapters are apparently written by others) aims "to outline the extent to which that knowledge (*i. e.*, of man and Nature) has now advanced in each of the major fields of scientific endeavor." Astronomy, physics, chemistry, geography, transportation, medicine, archeology, each is treated in a "march-of-time" manner, that offers many targets for the critic, both of selection of topic and of statements made. Yet, like its prototype, Science News Service, the book contains accounts of so many recent developments that there are few, indeed, even among scientists, who will fail to find much that is new and interesting. E. K.

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BODY MECHANICS. In the Study and Treatment of Disease. By JOEL E. GOLDTHWAIT, M.D., LL.D., Member of Board of Consultants, Massachusetts General Hospital, etc., LLOYD T. BROWN, M.D., Instructor, Orthopedic Surgery, Harvard Medical School, LORING T. SWAIM, M.D., Instructor, Orthopedic Surgery, Harvard Medical School, and JOHN G. KUHN, M.D., Assistant in Orthopedic Surgery, Harvard Medical School. Pp. 281; 99 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, \$4.00.

HERE are summarized in book form the teachings of Dr. Goldthwait. For many years the Boston group of orthopedic surgeons, under the leadership of Dr. Goldthwait, have dwelled at great length upon the value to all persons of the correction of faulty body mechanics. To the chronic invalid, regardless of the cause of his invalidism, they have held out the benefits which would result from the overcoming of defects in posture. That benefits would result is well known to the American orthopedists. Such knowledge is not had by the general practitioner. To him this book should be of great value in explaining "why" and telling "how."

G. W.

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BIOLOGY FOR MEDICAL STUDENTS. By C. C. HENTSCHEL, M.Sc. (LOND.), Lecturer in Zoölogy, Chelsea Polytechnic, etc., and W. R. IVIMEY COOK, B.Sc., PH.D. (LOND.), Lecturer in Botany, The University, Bristol, etc. With a Foreword by G. E. GASK, C.M.G., D.S.O., F.R.C.S., Professor of Surgery and Dean of the Faculty of Medicine in the University of London, etc. Pp. 618; 413 illustrations. New York: Longmans, Green & Co., 1932. Price, \$7.00.

"THIS book is primarily intended for the use of medical students in their first year in biology. It covers the syllabuses for the First M. B. Examination of the University of London, and also for the Pre-medical Examination for the Conjoint Examining Board in England of the Royal Colleges of Physicians and Surgeons. A notable feature is that both the Botanical and Zoölogical aspects of the subject are included in one volume." (Publisher's note.)

**ELEMENTARY HUMAN ANATOMY.** Based on Laboratory Studies. By KATHARINE SIBLEY, Professor of Physical Education, School of Education, Syracuse University. Pp. 360; 213 illustrations, many in colors. New York: A. S. Barnes & Co., Inc., 1935. Price, \$4.50.

"This text for an undergraduate [Dept. of Physical Education] course in human anatomy is written as a foundation for the study of kinesiology and physiology. The author has placed special emphasis on osteology, syndesmology, myology and the nervous system to aid the teacher of corrective physical education and physiotherapy in muscle examination and muscle reëducation. Each chapter is accompanied by laboratory studies and these studies are based on live muscles wherever possible." (Publisher's note.)

**THE CRIPPLED AND THE DISABLED.** Rehabilitation of the Physically Handicapped in the United States. By HENRY H. KESSLER. Pp. 337. New York: Columbia University Press, 1933. Price, \$4.00.

"Coming as it does in the midst of the largest national project for normal economic and social adjustment, . . . [this] book on the needs of the crippled and disabled should turn the attention of the socially minded to this unique problem.

"The popular fallacy that all disabled persons constitute a unit of sheer economic waste is quickly and totally dispelled. Physical limitations they may have, but the handicapped can be rehabilitated so as to become useful, self-supporting and responsible members of the community. Rehabilitation is, therefore, the key to the problem. Efforts for the reëducation of the community at large toward this unfortunate group must be met by legislative measures. A plea is made for more adequate and uniform legislation, so that all types of handicapped may be received by authorized state or federal agencies set up to adjust these individuals to the types of occupations peculiar to their specific disability.

"A detailed study is made of disabled persons classified according to type; this, together with perhaps the most comprehensive critical evaluation of the laws pertaining to this subject, comprise the basis of a book dealing with a vital problem." (Publisher's note.)

**THE PHYSICAL AND MENTAL GROWTH OF PREMATURELY BORN CHILDREN.** By JULIUS H. HESS, M.D., Professor of Pediatrics, College of Medicine, University of Illinois; Attending Pediatrician, Illinois Research, Cook County and Michael Reese Hospitals, GEORGE J. MOHR, M.D., Director, Pittsburgh Child Guidance Center, etc., and PHYLLIS F. BARTELME, Ph.D., Psychologist, Cook County Juvenile Court, Chicago; Research Psychologist, Institute for Juvenile Research. Pp. 449; 90 illustrations and 161 tables. Chicago: University of Chicago Press, 1934. Price, \$5.00.

PROGNOSIS is such an important aspect of clinical medicine that a monograph which furnishes reliable data is always welcome. Such a monograph is this by Dr. Hess and his associates. The Premature Infant Station of the Sarah Morris Hospital is well known to American pediatricians and they will find in this volume an immense amount of valuable material concerned with the immediate and remote prognosis of the infant prematurely born.

The book has been divided into three parts, but might just as well have been divided into two; the clinical studies by Dr. Hess on the immediate morbidity and mortality, together with the development and growth studies by Drs. Mohr and Bartelme, and the collection of previously pub-



lished papers by other associates. Indeed there is some doubt in the Reviewer's mind as to the propriety of including this latter material at all.

Dr. Hess' study of immediate mortality and morbidity and the etiology of prematurity is complete. Ample protocols of the necropsies of all fatal cases are available. Dr. Hess is to be congratulated that his results in the case of these babies become increasingly favorable.

A second division of the volume concerns itself with a statistical analysis of the fate, growth and development of the "graduates" of this Station. A wealth of material based upon careful studies of 250 children is presented from every aspect concerned with prognosis. The conclusions point out that early care and constant supervision have much to do with the results which seem more optimistic than those presented by other writers, such as Capper, Steinfuth and Yeggs.

Any reader seeking for information about the care of immature children will be disappointed with this book. Only two of the appended special articles deal with phases of that subject—anemia and the use of oxygen therapy. For those seeking information upon which to base prognosis this volume can answer any question.

E. T., Jr.

**HUMAN ANATOMY. DOUBLE DISSECTION METHOD.** By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. (First Dissection) 265, illustrated. Pp. (Second Dissection) 554, illustrated. New York: Columbia University Press, 1934. Price, \$3.00 each.

"THE time allowed for anatomy [in medical school curricula] has been very much reduced. Faced with this fact, a choice between two alternatives has inevitably been imposed; either to contract the former plan of teaching into half the time previously allowed—a method which places the students at a distinct disadvantage, or to create new methods to meet new conditions. The latter alternative is represented in the Double Dissection plan developed in the College of Physicians and Surgeons, New York. . . . The unusual features of the course form a 1-year course in anatomy of about 360 hours, which carries the students through two dissections of the entire body *with no greater expenditure of anatomical material than is ordinarily used*. The first dissection applies only to the larger structures, and gives students a preliminary understanding of those structures as a basis for the subsequent detailed dissection. The plan is designed for utmost economy in time and effort, with maximum pedagogic results." (Publisher's note.)

**THE CLINICAL ASPECTS OF VISCERAL NEUROLOGY.** With Special Reference to the Surgery of the Sympathetic Nervous System. By W. K. LIVINGSTON, M.D., Clinical Associate in Surgery, University of Oregon Medical School. Pp. 254; 46 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, \$5.00.

THE structure of the nervous system is much better known than are its functions. The author summarizes present-day knowledge by stating: "The function of the visceral nervous system is to regulate visceral activity so that the organism is brought into harmony with the ever-changing internal and external environment." It is this system which is intimately concerned with the maintenance of the "steady states" (to use Professor Cannon's happy phrase) which are characteristic of the higher forms of living creatures. There are a number of texts that deal with the visceral nervous system (the "vegetative," "involuntary," "autonomic," "sym-

pathetic and parasympathetic" system) from the standpoint of the experimental investigator; the present monograph deals primarily with clinical aspects. The first part of the book (pp. 5 to 58) is a summary of the anatomy and physiology; of particular interest to clinicians is the chapter on normal regulation of bloodvessel function and a discussion of visceral pains. The second part (pp. 59 to 130) deals with conditions that have been treated by visceral nerve surgery: functional disturbances and organic diseases of the arteries (such as Raynaud's disease, hypertension, thromboangiitis obliterans; angina pectoris), chronic arthritis and certain pelvic disorders. The third part of the monograph (pp. 131 to 226) is devoted to surgical procedure and general discussion. There are chapters on prognostic methods, surgical technique, surgical treatment of intractable pain, etc. The viewpoint of the author is expressed in the following quotation from the introduction: "It would be a mistake to consider sympathetic nerve surgery a panacea. On the contrary, cutting sympathetic pathways does not, as Sir Thomas Lewis has often reiterated, effect 'cures' in the sense that the underlying cause has been removed. The procedure might well be likened to the cutting off of lines of communication of an invading army. The fact that the communications have been severed does not destroy the army, but does handicap its advance, and may prove the means by which the tide of battle turns in favor of the defending forces." B. L.

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THE MEDICAL CLINICS OF NORTH AMERICA. VOLUME 18, No. 3 (NEW YORK NUMBER—NOVEMBER, 1934). Pp. 301; 17 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, per clinic year, July, 1934 to May, 1935, paper, \$12.00; cloth, \$16.00.

"A RADICAL change in policy is inaugurated with the publication of this number. Hereafter the *Medical Clinics* will feature the everyday 'run-of-practice' problems of the general practitioner. Emphasis will be placed upon diagnosis and treatment. The symposium idea will be further developed so that, insofar as possible, each number will contain a group of clinics dealing with the various clinical phases of some important diagnostic or therapeutic problem. Among the symposiums to be published during 1935 will be: 'The Treatment of Heart Disease,' 'Allergic Diseases,' 'The Medical Management of Biliary Disease,' 'The Treatment of Pneumonia.'

"These new *Medical Clinics* will present in detail certain definite clinical aspects of a condition, rather than general discussions. In other words, the *Clinics* will give the reader the clinical meat of a problem such as he would expect to obtain while in actual attendance at a postgraduate clinic." (From Publishers' Notice.)

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COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, VOLUME 2. Pp. 284; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1934. Price, \$3.35.

THE second volume of these symposia is chiefly concerned with various aspects of growth. Of the 34 articles presented only a few are by the authors included in Volume 1, though familiar names appear among those taking part in the discussion. A number of the presentations are on the chemistry of growth, genic factors and yeast; protozoa and amphibia as material for growth study. The necessary physical and mathematical backgrounds are also represented in some half dozen articles. We can only repeat our high praise of this effort to bring together in a novel way authorities in different fields of science in order to promote a discussion of biology that is as far as possible quantitative. E. K.

AN ATLAS OF THE COMMONER SKIN DISEASES. By HENRY C. G. SEMON, M.A., M.D. (OXON.), M.R.C.P., London, Physician for Diseases of the Skin, Royal Northern Hospital. Photography under the direction of ARNOLD MORITZ, B.A., M.B., B.C. (CANTAB.). Pp. 221; 103 colored plates. Baltimore: William Wood & Co., 1934. Price, \$12.00.

By a fortunate combination of the Finlay color photography method with the products of highly skilled engravers, this *Atlas* offers the best photographs in natural color of living subjects that the Reviewer has ever seen. Opposite each plate, abbreviated clinical descriptions and notes on differential diagnosis and treatment are given as *aides memoires*. In addition to the commoner skin diseases, 13 of the rarer forms are included. As far as the eye can contribute, these plates are as good as seeing the patient himself.

E. K.

THE JEW IN SCIENCE. By LOUIS GERSHENFELD. Pp. 224, Philadelphia: The Jewish Publication Society of America, 1934. Price, \$2.75.

THE present vogue for colorful biography, accentuated by the world's concern in a great nation's drive to rid itself of one of its most useful groups of citizens, arouses one's interest as soon as this title is read. The author, who "has interested himself for years in the history of science, Judaism and scientists," has not only given the high lights of a dramatic story of racial history in the first half of the book, but has furnished a useful reference work in the second half on modern Jewish scientists in medicine and other fields. As a reference book, it would be much more useful if the groups had not been rather arbitrarily and unsystematically subdivided or if an adequate index had been provided.

E. K.

ONE HUNDRED AND FIFTY YEARS OF PUBLISHING, 1785-1935. [HENRY CHARLES LEA.] Pp. 42; illustrated. Philadelphia: Lea & Febiger, 1935.

THOSE who have a penchant for long-lived institutions, and even believe that long life may contribute to their present efficiency, will be especially pleased with this record of one of the oldest publishing houses in the country. It is also one of the oldest firms in a city that has the largest number of firms in America that have been in continuous existence for over a century. Philadelphia can well afford to accept without rancor, even with pride, the chaffing that it may get from less stable sisters on such matters. Amplified from the sketch prepared by Henry C. Lea 50 years ago, our anniversary book describes the firm's activities and changes during 150 years. Especially picturesque is the account of its founder, Matthew Carey, an Irishman who came to this country in 1784, was "staked" in business by his friend, Lafayette (repaying the benefaction some 40 years later), wrote against duelling and later was wounded in a duel, brought his publishing firm into a leading position in this country, and founded (1820) *this Journal*, the oldest medical monthly in the country, and one of the very oldest medical periodicals in the English language. This journal (whose 11 editors are listed), the American edition of Gray's Anatomy (published since 1859) and Osler's "Modern Medicine" can perhaps be singled out from many successes as the firm's most important contributions to medicine. Of the 14 names that the firm has held, that of Henry C. Lea (1865-1880), one of America's greatest historians, is perhaps the most celebrated. The present senior member is fifth in direct descent from Matthew Carey. Long may the firm flourish in its business of furnishing "Quae prosunt omnibus."

E. K.

## NEW BOOKS.

*Diseases of the Mouth and Their Treatment.* A Textbook for Practitioners and Students of Medicine and Dentistry. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc., Dr. Med. Dent., Professor of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania, and SIGMUND S. GREENBAUM, B.S., M.D., Associate Professor of Dermatology and Syphilology in the Graduate School of Medicine of the University of Pennsylvania; Attending Dermatologist, Mt. Sinai and Philadelphia General Hospitals. Pp. 602; 287 illustrations and 11 colored plates. Philadelphia: Lea & Febiger, 1935. Price, \$9.00.

*Biology for Medical Students.* By C. C. HENTSCHEL, M.Sc. (LOND.), Lecturer in Zoölogy, Chelsea Polytechnic, etc., and W. R. IVIMEY COOK, B.Sc., PH.D. (LOND.), Lecturer in Botany, The University, Bristol, etc. With a Foreword by G. E. GASK, C.M.G., D.S.O., F.R.C.S., Professor of Surgery and Dean of the Faculty of Medicine in the University of London, etc. Pp. 618; 413 illustrations. New York: Longmans, Green & Co., 1932. Price, \$7.00. (Review, p. 574.)

*Elementary Human Anatomy.* Based on Laboratory Studies. By KATHARINE SIBLEY, Professor of Physical Education, School of Education, Syracuse University. Pp. 360; 213 illustrations, many in colors. New York: A. S. Barnes & Co., Inc., 1935. Price, \$4.50. (Review, p. 575.)

*Human Anatomy. Double Dissection Method.* By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. (First Dissection), 265, illustrated. Pp. (Second Dissection) 554, illustrated. New York: Columbia University Press, 1934. Price, \$3.00, each. (Review, p. 576.)

*Practical Neurological Diagnosis.* With Special Reference to the Problems of Neurosurgery. By R. GLEN SPURLING, M.D., Assistant Clinical Professor of Surgery (in charge of neurosurgery), University of Louisville School of Medicine. Pp. 233; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, \$4.00.

*The Jew in Science.* By LOUIS GERSHENFELD. Pp. 224. Philadelphia: The Jewish Publication Society of America, 1934. Price, \$2.75. (Review, p. 578.)

*The Crippled and the Disabled.* Rehabilitation of the Physically Handicapped in the United States. By HENRY H. KESSLER. Pp. 337. New York: Columbia University Press, 1935. Price, \$4.00. (Review, p. 575.)

*French Medicine.* Volume 15 of *Clio Medica*. By M. LAIGNEL-LAVASTINE, Professor in the Medical Faculty in Paris; Secretary General of the International Society of Medical History, and M. RAYMOND MOLINERY, Gold Medalist of the Academy of Medicine; Member of the French Society of Medical History. Translated by E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania. Pp. 187; 14 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$2.50.

*Mouth Infection.* Clinical Histories. By OLIVER T. OSBORNE, M.A., M.D., F.A.C.P., Professor of Therapeutics, Emeritus, and formerly Clinical Professor of Medicine, Yale University. Pp. 119. New Haven: By the author, 1934. Price, \$2.00.

A short summary with subject matter classified under three heads: (1) Teeth and gums; (2) tonsil infection; (3) Vincent infection, tongue, adenoid growths and the toothbrush.

F. W.

*The 1934 Year Book of Obstetrics and Gynecology. Obstetrics.* Edited by JOSEPH B. DELEE, A.M., M.D., Professor of Obstetrics, University of Chicago Medical School; Chief of Obstetrics, Chicago Lying-In Hospital and Dispensary in affiliation with the University of Chicago. *Gynecology.* Edited by J. P. GREENHILL, B.S., M.D., F.A.C.S., Associate Professor of Gynecology, Loyola University Medical School; Professor of Gynecology, Cook County Graduate School of Medicine, etc. Pp. 717; 96 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, \$2.50.

*The 1934 Year Book of Pediatrics.* Edited by ISAAC A. ABT, D.Sc., M.D., Professor of Pediatrics, Northwestern University Medical School; Attending Physician, Passavant Hospital, etc. With the collaboration of ARTHUR F. ABT, B.S., M.D., Associate in Pediatrics, Northwestern University Medical School; Adjunct Attending Pediatrician, Michael Reese Hospital, etc. Pp. 541; 74 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, \$2.25.

*Rats, Lice and History.* Being a Study in Biography, Which After Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals With the Life History of Typhus Fever. By HANS ZINSSER. Pp. 301. Boston: Little, Brown & Co., 1935. Price, \$2.75.

*The Care of the Aged, the Dying and the Dead.* By ALFRED WORCESTER, M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 77. Springfield, Ill.: Charles C Thomas, 1935. Price, \$1.00.

*Fracastor. Syphilis or the French Disease.* A Poem in Latin Hexameters. By GIROLAMO FRACASTORO. With a Translation, Notes and Appendix by HENEAGE WYNNE-FINCH, M.A. (OXON.), and an Introduction by JAMES JOHNSTON ABRAHAM, C.B.E., D.S.O., M.A., M.D. (DUB.), F.R.C.S. Pp. 253; illustrated. London: William Heinemann, Ltd., 1935. Price, 10/6.

*Surgical Diseases of the Chest.* By EVARTS AMBROSE GRAHAM, A.B., M.D., F.A.C.S., Professor of Surgery, Washington University School of Medicine, St. Louis; Surgeon-in-Chief, Barnes and St. Louis Children's Hospitals, etc., JACOB JESSE SINGER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician, Barnes Hospital, etc., and HARRY C. BALLON, M.D., C.M., F.A.C.S., formerly Assistant Professor of Surgery, Washington University School of Medicine; formerly Assistant Surgeon, Barnes Hospital. Pp. 1070; 637 illustrations. Philadelphia: Lea & Febiger, 1935. Price, \$15.00.

## NEW EDITIONS.

*Dietetics for the Clinician.* By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Department of Correction Hospitals, New York, etc. Foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University, New York. Pp. 970; 64 tables. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, \$10.00.

The first edition of this work was described by the Reviewer as deserving emphatic recommendation. His judgment has been confirmed by the popularity of the work which has led to a second edition within less than 2 years. The new volume, greatly amplified and in part rewritten, is an improvement on the first.  
R. K.

*Allergische Diathese und Allergische Erkrankungen.* By DR. HUGO KÄMMERER, Professor der Universität München, Leitendem Arzt der Inneren Abteilung des Nymphenburger Krankenhauses zu München. Pp. 359; 4 illustrations. Second edition, enlarged and improved. München: J. F. Bergmann, 1934. Price, paper, Rm. 26; bound, Rm. 29.60.

# PROGRESS OF MEDICAL SCIENCE

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## GYNECOLOGY AND OBSTETRICS

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UNDER THE CHARGE OF  
CHARLES C. NORRIS, M.D.,  
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,  
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND  
FRANK B. BLOCK, M.D.,  
SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

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### OVARIAN TUMORS.

PROBABLY the most common complication of all ovarian tumors is torsion or twisting of the tumor on its pedicle, and while many theories have been advanced as to the cause of this phenomenon, it still remains in the field of speculation. Shaw<sup>1</sup> states it to be a well-established clinical fact that a history of exertion or violent movement is frequently obtained in cases of torsion. It is suggested that these movements result in a rotation of the tumor through half a circle or more. In cases which arise independently of such movements, similar small twists may be induced through movements of the sigmoid or rotations of the body of the patient, such as turning over in bed. He suggests that the next factor in the production of torsion is hemodynamic. However slight the torsion of the ovarian tumor, the ovarian artery must be both stretched and twisted. Most important of all, the twist of the artery is in the same direction as the original twist of the cyst. The twisted artery pulsates, for in the original stage of torsion the lumen of the vessel is not obliterated. With each pulsation a column of blood, the dimensions of which are determined by the lumen of the artery, is forced through the artery. As the wall of the vessel is twisted, part of the momentum of the blood is spent against the wall and the force exerted will always be in the direction of the twist. In other words, the pedicle of the cyst is subjected to a series of small impulses, each of which tends to increase the extent of the twist. Though each impulse is extremely small, the combined effect of the impulses in rotating the tumor, recurring 72 times per minute, will be considerable. The tumor itself is free to move and pain develops when the veins become occluded and the tumor becomes engorged with blood. On this theory further torsion will cease as soon as the main artery in the pedicle is occluded. It should be remembered that torsion is often spontaneously reduced, which is rather difficult to explain under the above theory, although, of course, it is doubtful if

cases in which there are extreme degrees of torsion ever reduce themselves spontaneously.

**Carcinoma.** In a group of 403 cases of adenocarcinoma of the ovary in which operation was performed at the Mayo Clinic, Moench<sup>2</sup> states that 254 were papillary cystadenomas, 72 carcinomatous cystadenomas and 77 solid adenocarcinomas. The incidence of adenocarcinoma of the ovary is highest in the fifth and sixth decades of life. There are no characteristic symptoms of this disease. Abnormality of ovarian function was apparent through disturbance of menstruation evidenced by recent change in periodicity, profuse flow, scanty flow or metrorrhagia. Pain was an outstanding symptom in over half of the cases. Three years after operation nearly 60% of the patients were living, the best results being obtained in those patients who had papillary cystadenoma. In a fourth of the patients the tumor was bilateral and in these the length of life after operation was shorter and only half as many survived the 3-year period as when the tumor was unilateral. Intracystic malignancy was less likely to recur than extracystic malignancy. Of the patients who had metastases, 30% were living 3 or more years later, the results being better in those who had only pelvic metastases compared to those who had both pelvic and abdominal involvement.

In a study of the incidence of malignancy of the ovary in the first 3 decades of life, Schreiner and Wehr<sup>3</sup> found that of 2405 gynecologic malignancies admitted to the State Institute for the Study of Malignant Disease at Buffalo, 114 (4.6%) occurred during this period, and of these, malignancy of the ovary represented 10.6% (23 cases). Of these, 6 were papillary cystadenocarcinomata, 6 adenocarcinomata, 9 carcinomata, 1 sarcoma and 1 malignant teratoma. Two of the cases were between 10 and 15 years of age, 3 between 16 and 20, 8 between 21 and 25 and 10 between 26 and 30. Of the 23 patients, 13 were unmarried, while 2 of the married patients had no pregnancies. These figures should remind us that the so-called carcinoma age may begin early in life rather than at 40 as so often inferred.

**Granulosa Cell Tumors.** The gynecologic literature for the past few years is fairly teeming with discussions about ovarian tumors which are associated with changes in the secondary sexual characteristics. While these tumors are not common, they are apparently more frequent than was formerly believed and have been found by several pathologists in checking back on old slides in which they were originally missed. In discussing granulosa cell tumors Novak and Long<sup>4</sup> state that it is commonly believed that they arise from the early oöphorogenic structures in the sex gland area. The evidence seems to point to the fact that the real germinal epithelium of the ovary is derived from the mesenchyme of the sex gland anlage. This is contrary to the previously accepted view that the follicular apparatus is the result of downgrowth of the germinal epithelium covering the ovary into the mesenchyme beneath in the form of medullary cords. In either event there is further differentiation of the cells of the sex cords into two types, one becoming the oögonia, the other the follicular epithelium, the latter grouping themselves around the egg cells to form the primordial follicles. In this process, rests of granulosa cells may be left over and from them the granulosa cell tumors arise and not from the granulosa cells of the adult follicles.

The granulosa cell is a typically feminine cell, producing the female sex hormone (folliculin or theelin); therefore, the effects produced by this type of tumor are along the lines of feminization, with overaccentuation of certain female sex characters and functions. When the tumors arise in elderly women, as they usually do, they produce a remarkable effect on the uterus, through the endocrine action of the granulosa elements. The uterus becomes characteristically increased in size and pseudomenstrual bleeding is noted, so that in some cases women far beyond the menopausal age exhibit an apparent reestablishment of the menstrual function. This sequence must, therefore, be kept in mind as a possible explanation of postmenopausal bleeding. If diagnostic curettings in such cases show no suggestion of malignancy, but on the other hand reveal typical hyperplasia of the endometrium, the first thought should be of granulosa cell tumor of the ovary. (Curetting may also exhibit the normal cyclic changes despite the fact that the patient may have been long past the menopause.—C. C. N.) In a few cases, granulosa cell tumors have occurred in children, producing remarkable hormonal effects. The hyperfeminizing influence of these neoplasms is shown by the fact that in young children precocious puberty and menstruation are produced together with such secondary sex characters as mammary hypertrophy, the growth of genital and axillary hair, increased growth, the development of the typical feminine postpuberal contour and increased size of the uterus. Although these tumors are malignant, the degree of malignancy is in most instances very low and recurrences are exceptional, even after the removal of only the affected ovary. In a certain proportion of cases, however, the tumors have run an extremely malignant course with recurrence, metastasis and death. Such a course has been noted in between 5 and 10% of reported cases.

Schulze<sup>5</sup> has found 4 cases of granulosa cell tumor among 43 ovarian carcinomas occurring in 7500 gynecologic cases over a period of 19 years and has had 2 other specimens brought in from outside sources. Four of the specimens were originally diagnosed as medullary carcinoma, by competent pathologists. She states that this error is not uncommon, since the microscopic illustrations of medullary carcinoma or solid carcinoma in almost any of the standard texts may be taken as fairly typical examples of the cylindroid type of the granulosa cell tumor. These tumors are usually unilateral and the majority are comparatively small in size, varying from almost microscopic ones discovered accidentally to those of the size of a man's head. They are usually well encapsulated with a thick, fibrous capsule. On cut section there appear macroscopic cysts the size of a pea, rarely up to the size of a hen's egg, containing fluid, sometimes clear, in others greenish and turbid. The greater part of the tumor is usually solid, moderately firm, sometimes friable and very vascular. Microscopically there are 3 types, the folliculoid, the cylindromatoid and the diffuse or sarcomatoid. The most easily recognizable type, and the one in which the morphologic resemblance to the normal granulosa cell is most striking, is the folliculoid and it is also the rarest. The cylindromatoid tumors are far more common but are much more difficult to recognize. They are frequently diagnosed as medullary carcinoma or solid carcinoma or even as endothelioma or sarcoma. In a few cases there may be a diffuse picture resembling a sarcoma. The epithelial cells lose their



normal characteristics and become rather hard to differentiate from the stroma cells which may show a sarcomatoid proliferation. A careful study of the patient from the endocrine standpoint will prove of aid in the pre-operative diagnosis as well as in postoperative prognosis, since these tumors elaborate follicular hormone. Schulze believes it is probable that the follicular hormone tests will become as important for these cases as is the Aschheim-Zondek test for chorionepithelioma.

An interesting case of granulosa cell tumor in a child, aged 7, who showed sexual precocity has been reported by Bland and Goldstein.<sup>6</sup> This child menstruated regularly, had enlarged breasts and pubic and axillary hair. She came to the hospital because of an enlargement of the abdomen and at operation a large tumor of the left ovary was removed which proved to be a granulosa cell tumor. The right ovary appeared normal and was left *in situ*. Following the operation the child did not menstruate for 18 months. The menses then returned, the abdomen again enlarged and she developed pain in the right side. At operation a tumor was removed on the right side similar to the one which had been removed on the left. She made a satisfactory recovery and on the 14th day after operation the estrin and Aschheim-Zondek tests, which had been positive before operation, became negative. Six months later, although the estrin test remained negative, there had been no regression of the mammary development and pubic and axillary hair was present in abundance.

For those especially interested in these tumors the paper of Brewer and Jones<sup>7</sup> reporting 3 cases and that of Daily<sup>8</sup> presenting 2 cases may be consulted for further case details.

In considering the treatment of these tumors, Novak and Brawner<sup>9</sup> state that it is essentially surgical. The extent of the operation must be based upon our concept of the degree of malignancy which is conceded less than that of other ovarian neoplasms. Many patients have remained well after simple unilateral salpingoöphorectomy, but they believe that such a conservative plan should be followed in only a limited group in view of the fact that recent reports indicate a greater degree of malignancy than had been previously assumed. In young patients the removal of the adnexa on the affected side alone would seem permissible, but such patients should be carefully followed for evidence of recurrence. In the more common case, in which the patient has already lived all or most of her reproductive life, the definite menace presented by these tumors would seem to justify a more radical procedure, namely, hysterectomy with bilateral removal of the adnexa. This would certainly apply to the frequent cases seen in women beyond the menopause. In view of the sensitivity of granulosa tissue to radiotherapy, it would be expected that these tumors should likewise be very responsive to this form of treatment, although only a few reports have been made on this point. They believe, however, that for the present it should seem wiser to restrict radiotherapy to the treatment of inoperable or recurrent tumors, or to combine it pre-operatively or postoperatively with surgery in the treatment of removable tumors.

**Krukenberg Tumor.** This neoplasm to which the unwieldy name, "fibrosarcoma ovarii mucocellulare (carcinomatodes)," is applied should be of passing interest to every practitioner if for no other reason than its name. Krukenberg described it as a fibrosarcoma and believed

that it was primary in the ovary, although there has been considerable discussion about this. In presenting 3 cases of this type Andrews<sup>10</sup> states that it is a solid ovarian tumor, usually bilateral, maintaining the contour of the ovary. It is pale gray and heavy, usually associated with ascites. The microscopic picture is that of a dense fibrous tissue in the meshes of which are the characteristic cells with nuclei displaced eccentrically, giving a signet-ring appearance. The tumor is generally regarded as a carcinoma. At present most authorities concede that these tumors are always secondary to carcinoma in the upper abdomen but the mode of transmission is not definitely settled, since some believe it arises from direct implantation on the ovary while others believe it is transmitted by lymphatic channels.

Based upon 5 certain and 7 additional probable cases of Krukenberg tumor which have been seen at the Mayo Clinic, Masson<sup>11</sup> is also of the opinion that these tumors are usually bilateral and retain the form of the ovary. They are probably always secondary. Of the patients in this series whose subsequent history is known, all have died of the disease. He feels sure that in many cases of general abdominal carcinomatosis in which exploration is made late in the disease, the typical pathologic change in the ovarian tissue is not evident. The picture is obscured by necrosis and cystlike formations, which develop because circulation for the rapidly growing tumor is inadequate. Furthermore, ovarian tumors are often removed as solid carcinomas or sarcomas, and when death ultimately occurs, as it invariably does in this condition, necropsy is not performed, and death is credited to recurrence of the ovarian tumor, or to metastasis from it. If necropsy had been performed, in many of these cases a malignant growth in the gastrointestinal tract probably would have been found. He believes that these tumors are of more frequent occurrence than the literature would indicate, for they are seldom diagnosed before operation or necropsy and often not even then. (When operating upon patients for ovarian neoplasm, especially if the tumor is thought to be malignant, the entire peritoneal cavity should be explored.—C. C. N.)

Presenting a Krukenberg tumor with rectal involvement, Runyeon<sup>12</sup> states that such a complication is very rare, only a few having been reported in the literature. In reviewing Krukenberg tumors in general, he has collected 91 cases in 23 of which only the ovary was involved. He asks, therefore, why it is necessary that the ovarian picture must always be a secondary one. He believes that a carcinoma of this type may originate in the ovary primarily in certain cases, and by its presence stimulate the connective tissue cells of the ovary to the same growth that is produced by a carcinoma originating in the stomach and secondarily involving the ovary. This is, of course, contrary to most opinions.

**Arrhenoblastoma.** A rare but exceedingly interesting tumor, which at times produces effects on sex characters almost diametrically the opposite of those resulting from granulosa cell tumors, is the arrhenoblastoma, which has a masculinizing effect on the patient. Novak and Long<sup>4</sup> state that the histogenesis of these tumors is to be sought in certain undifferentiated cells persisting in the rete and capable of later function along either male or female lines. To put it another way, every woman shelters within the medulla of the ovary a potential testis. Under certain conditions this undifferentiated male tissue may become active, and its male endocrine influence may override the primary

female tendency. The clinical manifestations of these tumors vary according to the degree of their masculinizing hormonal influence, and this in turn appears to be a reflection of the degree of undifferentiation of the tumor cells. In the most extreme cases the woman who has previously been of normal feminine type becomes amenorrheic, the breasts flatten and atrophy, a heavy growth of hair appears over the face, chest, abdomen and lower extremities, the figure loses its normal feminine curves and assumes the typically more angular contour of the male and the voice becomes much deeper, owing to laryngeal hypertrophy. The clitoris may show such hypertrophy as to be almost penis-like in its proportions. Such symptoms occurring in a patient who has developed an ovarian tumor should lead to the suspicion that one is dealing with an arrhenoblastoma. Removal of the tumor leads to a regression of the symptoms, thus establishing its causative rôle. Tumors of this general group are usually unilateral and, like most tumors of this embryonic group, are of a relatively low degree of malignancy. Only a small group of these tumors has been reported, but with new interest in the syndrome there is little doubt that the number will be rather rapidly augmented. The case reported by Mathias<sup>13</sup> is of especial interest in that after removal of the tumor there was a subsequent pregnancy, there being only 4 similar cases in the literature. In this case a girl, aged 17, had an amenorrhea of 2 years' duration, during which time masculine characteristics developed, including a growth of beard, male type of pubic hair, loss of feminine contour, alteration in voice and enlargement of the clitoris. After the removal of an arrhenoblastoma, most of the secondary male characteristics disappeared. The patient subsequently conceived and was delivered by section because of the male type of pelvis.

**Other Rare Tumors.** A third type of tumor which alters the sexual characteristics of the afflicted person, differing from both the granulosa cell tumor and the arrhenoblastoma is the theca cell tumor or "fibroma thecocellulare xanthomatodes ovarii." Two cases of this type have been reported by Melnick and Kanter,<sup>14</sup> who state that there have previously been reported only 6 similar cases. These tumors are of the feminizing type and, like the granulosa cell tumors, produce glandular hyperplasia of the endometrium, together with more or less periodic bleeding in postmenopausal women and amenorrhea in younger women. Such effects are undoubtedly due to the secretion of estrogenic hormone by the tumor. The site of origin of this hormone (theelin) is still a point of discussion. The Graafian follicle, particularly the granulosa cells, has been considered to produce the hormone, but these authors believe that there is much evidence that the cells of the theca interna play a rôle in its production. While the function of the theca interna has been much of a mystery, its activity in the ripening follicle, in the young and degenerating corpus luteum and in the atretic follicle indicates that it has a possible function. In the cases described, the tumors arose from the cells of the theca interna and since they exerted a distinct hormonal effect, they believe that the theca cells take part in the production of theelin.

The occurrence of a *squamous-cell epithelioma* in a *dermoid cyst* of the ovary is unusual. Counseller and Wellbrock<sup>15</sup> found 7 (1.7%) in a series of 408 dermoid cysts which proved grossly and microscopically to be associated with primary epithelioma of the epithelial elements

of the cyst. Of passing interest it may be noted that 88 of the other cysts contained only sebaceous material; 192, sebaceous material and hair; 76, teeth in addition; while 45 contained hair, cartilage, bone and calcareous material. Discouraging upon the confusion that exists as to the proper classification of dermoid cysts, they believe that they are properly classed as cystic teratomas. A true dermoid cyst is a distinctly inclusion cyst, such as those seen in the coccygeal, perineal and branchial regions and contains products from the ectoderm only, whereas the cystic teratoma contains tissues derived from one or all three germinal layers. Solid teratomas resemble the cystic teratomas in that they are usually composed of all three germinal layers. The true point of distinction is that the tissues composing the solid teratomas are of the early embryonal stage and do not reproduce the highly developed and differentiated bodily structures which may be seen in the cystic tumors. The solid teratomas are much rarer than the cystic and are extremely malignant. The Reviewer recalls the only case of solid teratoma which he has seen and which recurred as an extensive growth within a month after removal of the primary tumor.

In reporting an *ovarian tumor which contained thyroid tissue* Lyday<sup>16</sup> states that, although the incidence of this type is supposed to be about 2% of all ovarian tumors removed, a relatively small number have been recorded in the literature. The case he reports is that of a girl, aged 19, in whom an ovarian tumor was discovered by routine examination. At operation a large multilocular cyst of the left ovary, weighing 8½ pounds, was found. At the base of the tumor near the pedicle was a solid portion, about 2 inches in diameter, which upon microscopic examination showed typical thyroid tissue. There were no symptoms in this case referable to hyperfunction of thyroid tissue.

*Fibroma of the ovary*, while a benign tumor, is often confused with a malignant condition because it is frequently accompanied by an ascites. An interesting case has been reported by Marshall and Swanton.<sup>17</sup>

**Prognosis of Ovarian Cancer.** According to Judd and Phillips,<sup>18</sup> on opening the abdomen in a case of carcinoma of the ovary, a surgeon's first impression may be that the malignant process is too extensive for the condition to be remedied. However, in many instances careful dissection will afford a chance for palliative relief and in such cases the patients have lived over 5 years. Even in the most hopeful cases, adequate treatment will include removal of the uterus, tubes and ovaries. Metastasis is usually by direct extension or by implantation. Papillary cystadenomas, in particular, have a tendency to rupture early in their course, and numerous nodular growths may develop. If secondary growths are present, as many as possible should be removed. In some cases the body of the uterus will be involved; therefore, hysterectomy should be included in any operation. If there should be a recurrence of the pelvic tumor at some later date, a second operation may be justified. Often removal of such a lesion will so completely control the disease that the patient is able to live for the normal span of life. They believe that the prognosis depends on many factors. The grade of the ovarian malignancy is one of the important determinants, since each of 2 patients who had adenocarcinoma of the ovary, graded 1, has lived more than 16 years since operation. An intracystic process is more likely to be controlled than one that is extracystic. In both cases in which the tumor was graded 1, the condition was bilateral,

and in one of these the growth was not only extracystic but had ruptured and produced multiple implants. It has been shown that in about 25% of the cases the disease will be bilateral. Because of the lapse of this length of time, and because both of these patients are entirely well at present, they believe that they will continue to be free from the disease and will have many additional years to live, as they are now aged only 51 and 52 years.

**Irradiation Therapy of Ovarian Cancer.** Backed by a most extensive clinical experience, Healy<sup>19</sup> is of the opinion that ovarian tumors should be treated surgically unless there is some contraindication to operation, since it is often difficult to differentiate clinically between a benign and a malignant ovarian tumor and surgical removal of the former should always result in cure. If at operation the tumor is found to be malignant but is apparently completely removed, post-operative irradiation of the entire pelvic and tumor field with high-voltage Roentgen ray should, nevertheless, be done within from 4 to 8 weeks. Such treatment should always include the line of incision, because of the frequency of incisional recurrences from implantation metastases. This series of Roentgen ray treatments should be repeated 2 or 3 months later. If the tumor is malignant, and at operation is only partially removed or not removed at all, intensive postoperative irradiation of the entire tumor field with high-voltage Roentgen ray should be established as soon as the condition of the patient will permit. If the tumor masses respond to radiation but do not disappear, the series of treatments should be repeated as soon as the condition of the patient's skin in the irradiated fields will permit and as often thereafter as may seem to be necessary. If the clinical findings indicate that the tumor is probably malignant but is too extensive for operation, radiation therapy with high-voltage Roentgen ray or the radium pack should be intensively carried out. If thereafter sufficient improvement is obtained, surgical interference may be then instituted. Tumors complicated by large quantities of free fluid or metastases should be intensively irradiated and observed for a time before resorting to exploratory operation, as the tumor masses will, in many instances, diminish markedly in size and occasionally may disappear entirely. Free abdominal fluid, if present in sufficient quantity, should always be removed by paracentesis before radiation treatment is given and as often as may be necessary during the course of treatment.

Montgomery and Farrell<sup>20</sup> have analyzed 22 cases of ovarian carcinoma according to type, grade of malignancy, operability and response to postoperative Roentgen ray treatment. Of 11 patients observed more than 5 years, 5 (45.4%) are alive. Of 14 patients with papillary cystadenocarcinoma, 7 are living and 7 are dead; 3 patients had papillary adenocarcinoma, 1 is living and 2 are dead; 4 patients with adenocarcinoma are dead; 1 patient with granulosa cell carcinoma is living. In order of malignancy, the granulosa cell is the least malignant, the papillary cystadenocarcinoma the next, the papillary adenocarcinoma is more malignant than the preceding and the adenocarcinoma is the most malignant. They also believe that the histologic grading of malignancy is important in the prognosis of ovarian cancer. Only 1 patient in their series whose tumor was of high-grade malignancy has survived for more than 5 years; all others with tumors of intermediate or high-grade malignancy are dead. They state the obvious fact that the more

completely operable the tumor, the greater the life expectancy, and they have also found that postoperative Roentgen ray irradiation is often of value in relieving pain and ascites and in reducing the size of the tumor. A comparison of this series of patients treated with postoperative irradiation and a group treated by operation alone indicates that the duration of life is longer in the irradiated patients, so that they urge postoperative irradiation in every case, no matter how hopeless the prognosis, if the general condition of the patient will permit. In the discussion of this paper Keene presented his observations on 38 cases which he divides into 3 groups: (1) Advanced lesions with advanced peritoneal carcinomatosis, in which the primary growth could not be removed; (2) removable growths, but peritoneal metastases present; and (3) the early cases where the growth could be completely excised and there was no visible evidence of extension. Twenty-one patients are dead and all belonged to Groups 1 and 2. In 90% of these, death occurred in 2 years or less after the beginning of their treatment. In his experience the histologic grading has been of little or no value in prognosis. He found that postoperative irradiation diminished or relieved pain in 60% of the cases. Ascites was present in 22 cases, and in one-third of these accumulation was retarded, thus lengthening the interval between tappings and, in a few, it was entirely checked. Abdominal masses were reduced in 30% and in some they completely disappeared for a time. These results seem to justify the conclusion that Roentgen ray irradiation is of value as a palliative measure. His experience has also shown that even in the presence of peritoneal metastases, the primary growth should be removed whenever possible. The advisability of combining deep Roentgen ray therapy with operation in the early cases is still controversial, but the evidence at hand strongly indicates that by combining the two, the total 5-year salvage will be increased.

In this same discussion Widmann stated that at the Philadelphia General Hospital they have not discovered anything that will control the untoward symptoms which accompany intensive irradiation. Intravenous glucose and sometimes normal saline seem to have been beneficial. He does not believe that anemia is a contraindication to irradiation, since patients with red blood cell counts as low as 2,000,000 and a hemoglobin as low as 25% will tolerate radiation given cautiously. On the other hand, a white blood cell count less than 3000 seems to be the most decided contraindication. In the very profound anemias he believes it worth while to consider transfusion for transient benefit.

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## DERMATOLOGY AND SYPHILOLOGY

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## TUBERCULOSIS OF THE SKIN.

### RECENT PROGRESS IN THEORY AND PRACTICE.

**Pathology and Immunology.** The principal contributions of the past 2 years in this field have included a further report by Kren and Lowenstein<sup>1</sup> on the cultivation of tubercle bacilli in the blood of patients with various forms of clinical tuberculosis and tuberculid; the discussion of the significance of anergy in relating such conditions as sarcoid of Boeck to cutaneous tuberculosis (Jadassohn<sup>2</sup>); the observations of Kallos and Nathan<sup>3</sup> on some cultural peculiarities of the tubercle bacillus from human cutaneous tuberculosis; the significance of the epicutaneous or tuberculin patch tests in diagnosis and as a measure of tuberculin allergy by Hruszek<sup>4</sup> and Sipos;<sup>5</sup> and finally the discussion conducted at the reunion in Strasbourg by a large group of French-speaking dermatologists on the etiology of sarcoid and its possible relations to tuberculosis and other conditions.

Summarizing this work, it appears that Kren and Lowenstein, who originally announced 75% positive cultures of tubercle bacilli from the blood by a special method in cutaneous tuberculosis of various types, have conducted 377 further examinations of 101 cases of cutaneous tuberculosis and 32 cases of lupus erythematosus. These authors contend that the usefulness and applicability of their method has been supported by other reports in the literature, including 18 positive cultures in cadaver blood and 12 from the blood of living patients with cutaneous tuberculosis. They obtained in their second series 51.8 positive cultures; 20% positive on a single trial and 100% positive on cases subjected to 4 cultural attempts. This work must be rated as still unconfirmed. Jadassohn,<sup>6</sup> both in independent publication and before the Strasbourg reunion, pointed out the striking resemblances between the characteristic anergic cutaneous reactions to tuberculous

inoculation in rats and human sarcoid. He pointed out that not only did tubercle bacilli rapidly disappear from the site of inoculation in an anergic animal or individual, but that the organisms which remained were rapidly changed in morphologic characteristics. The histologic reactions were very suggestive of sarcoid. He, therefore, considers that it is justifiable to interpret human Boeck's sarcoid as a form of anergic tuberculosis in man. Kallos and Nathan showed that only the serum of patients with cutaneous tuberculosis can inhibit growth and change the morphology of tubercle bacilli cultivated in cutaneous lesions. Serum from patients with pulmonary tuberculosis has no effect. The serum from patients with lupus erythematoses and Boeck's lupoid had no effect on cutaneous strains of tubercle bacilli. The work was performed on laboratory strains and could not be confirmed on tubercle bacilli cultivated directly from the human cutaneous lesions.

The observations of Kallos and Nathan on the specificity of patch test performed with 10% old tuberculin on patients with cutaneous tuberculosis as a means of diagnosing tuberculous lesions, have been subjected to further study, and the prevailing opinion is that the tuberculin patch test, when positive, is a measure of the grade of allergic susceptibility to tuberculin in the individual but does not require the presence of a cutaneous tuberculous lesion for a positive reaction.

**Epidemiology.** Ledermann,<sup>7</sup> in studying the incidence and proportion of tuberculosis of the skin in the clinics of Breslau, made the observation that there was a marked decrease in fatality of tuberculosis in Prussia up to the time of the World War (31 per 10,000 to 14.5 per 10,000) with a reversal of the trend or increase of frequency following the war. In Breslau there was a marked increase of both cutaneous and glandular tuberculosis from 1913 to 1919, with a recession following the siege of 1918-1920. Tuberculosis verrucosa cutis, however, was an exception and did not increase in frequency because of the war. The author pointedly remarks on the unreliability of epidemiologic figures based on clinic attendance, for it was distinctly observed that the picture of tuberculosis as seen in the clinics was influenced by the movement of physicians back to the country after the war, with corresponding changes in clinic attendance.

**Various Clinical Types of Cutaneous Tuberculosis.** *Erythema Nodosum.* The relation of the more or less non-specific clinical picture of erythema nodosum to tuberculosis is arousing widespread interest. For a number of years the closeness of this relationship in infants and young adults exposed to tuberculosis has been more or less recognized, but lacked precise definition. In an editorial in the *Lancet* (2, 660, 1934), the entire problem is reviewed. Four types of the condition are recognized: (1) A form which may be regarded as an infectious disease *sui generis* and more properly called nodal fever; (2) a type associated with acute or subacute rheumatism; (3) the tuberculous type; (4) a type due to various toxins, especially from streptococci. Slot<sup>8</sup> believes that in London at least the majority of cases are due to streptococcal and not to tuberculous infection. This view is vigorously opposed by Forman and Whitwell,<sup>9</sup> of Guy's Hospital, who quote Symes as finding that 10% to 20% of erythema nodosum patients subsequently developed tuberculosis, the period of greatest danger being 6 months after the appearance of the nodes. Symes quotes the Scandinavian incidence as being in some cases as high as 50%, but most frequently 10% to



30%. He cites Wallgren,<sup>10</sup> who obtained tuberculous infections in guinea pigs by inoculating them with the washings of the stomachs of children with erythema nodosum. The fact that the erythema nodosum precedes the appearance of frank tuberculosis explains the relative rarity of the condition in the frankly tuberculous individual. Lendon observed 40% phlyctenular conjunctivitis in his cases and Symes, 10%. Forman and Whitwell conclude that erythema nodosum is a reaction to bacterial allergy and do not subscribe to the rheumatic or streptococcal etiology so far as England is concerned. They point out the futility of pathologic and bacteriologic studies of the nodes because of the presumed small number of the bacilli and the rapid bacteriolysis which occurs in the inflammatory allergic reaction. The frequent initial severe sore throat these authors believe activates the tuberculous focus. They subscribe to Ranke's view that erythema nodosum is a secondary tuberculous manifestation with the probable course of events including a primary inoculation with tubercle bacilli usually *via* the respiratory tract, but occasionally through the skin or other structures. The patient becomes acutely allergic as a result of this inoculation, where erythema nodosum ensues, but in the case of miliary tuberculosis a depressed sensitivity to tuberculin develops. Comparing the child with erythema nodosum with the adult with erythema induratum, the authors believe that erythema nodosum is a manifestation of a high degree of allergic susceptibility, while the chronic erythema induratum, in which tubercle bacilli have been found, is an expression of late slight allergic reaction in a patient primarily infected years before.

In the Scandinavian countries the acceptance of erythema nodosum as tuberculous is apparently quite general, whereas the German school is inclined to oppose the conception. Giertsen<sup>11</sup> studied 93 cases in Bergen, from 1924 to 1931, of which 87% were between the ages of 15 and 30; and a marked adenitis at the hilus of the lung was found in 80% of 89 patients. In 48 of these cases pulmonary infiltration or pleurisy was found within the first month after the appearance of the erythema nodosum. Pathologic changes at the apices were rare. The Pirquet test was positive in 46 of 47 cases. The sedimentation test was very valuable, an increased rate of sedimentation more than a month after the nodes had appeared being interpreted as evidence of active disease of the lungs or pleuræ.

Ernberg<sup>12</sup> has studied 200 cases of erythema nodosum at the Sachs Children's Hospital in Stockholm, and concludes that erythema nodosum is to be regarded in general as a symptom complex of tuberculous nature. The focus is usually in the region of the pulmonary lymph nodes. It is essentially an autogenous tuberculin reaction, characterized by a general, local and focal phase, including fever, the characteristic eruption, and a focal reaction in the hilar region. It appears most often as a very early stage of tuberculosis in the transition from the pre-allergic to the allergic state. In some cases an infectious disease may precipitate the allergic condition. In treatment it is important to estimate the condition of the pulmonary lymph nodes. The prognosis is usually favorable, and it is frequently possible to trace the source of infection to a formerly unknown carrier, namely, a person with open tuberculosis. Rotnes<sup>13</sup> publishes independently confirmatory evidence of the open tuberculous source of infection in erythema nodosum in his description of a "family epidemic," in which 4 sisters living together,

2 children and 2 adults suffered within 5 weeks from acute and typical erythema nodosum. In both children a probable fresh lung infection was detected radiologically. Both adults were free radiologically. All 4 gave strong cutaneous tuberculin reactions. Shortly before the attack, 1 child and 1 adult had been found Pirquet-negative and also with lungs free radiologically. No throat or rheumatic symptoms were found in any case. The tuberculous husband of 1 of the grown-up sisters had recently come to live in the house, and before his death, a few months later, he infected 3 children additional to the above. The author concludes that the erythema nodosum was of the same nature in all 4 cases; that tuberculous infection was an essential condition for its development and that in no particulars did it differ from classical "idiopathic" erythema nodosum. In Cruise's<sup>14</sup> careful study of 33 cases of erythema nodosum in pupil nurses,  $\frac{1}{3}$  either developed definite tuberculosis or were suspicious of tuberculosis either at the time of the eruption or within 6 months; and over  $\frac{1}{2}$  had erythema nodosum during or after their affiliation with an institution for the treatment of tuberculosis. Cruise, as a result of this investigation, rates erythema nodosum as fully as much a manifestation of tuberculosis as pleurisy with effusion. One nurse developed active tuberculosis of the lungs within 6 months after having acute erythema nodosum and succumbed within another year. Similar cases have been mentioned in the American literature during the past decade, and Holmes<sup>15</sup> states that in the Frederiksborg Hospital, Copenhagen, in Pirquet-negative nurses exposed to tuberculous infection, 22.1% developed erythema nodosum within 7 months from the first date of exposure. This résumé does not by any means include the full roster of publication during the past several years on this topic, so that the volume of evidence for a tuberculous factor is larger even than here presented.

*Primary Inoculation Tuberculosis.* The rather scanty literature on this subject is reinforced by a careful report from Siegl.<sup>16</sup> The 5 children all presented negative pulmonary examinations, both clinical and radiologic, blood stream infection was excluded and the conspicuous and sharply reactive lymphatic metastasis was easily identified. Siegl believes that a negative tuberculin test does not exclude systemic tuberculosis in these cases, but points out that the clinical picture of primary inoculation tuberculosis is easily recognized by the very marked lymphadenitis, which does not occur in local inoculation of the exogenously infected tuberculous child (as in the case of tuberculosis verrucosa from thumb sucking which he cites). In tuberculosis verrucosa cutis, no regional lymphadenopathy is observed. The article is accompanied by a number of excellent illustrations. Ledermann<sup>17</sup> disagrees on the matter of local lymphadenopathy which he says is marked in tuberculosis verrucosa cutis. This form of inoculation tuberculosis was found to occur chiefly in farmers and laborers, usually on the hands, and to be, in 60% of cases, of the bovine type.

*Lupus Erythematosus.* The relationship of this condition to tuberculosis was studied by Keil<sup>18</sup> on the basis of the recorded 125 post-mortem examinations of patients with lupus erythematosus, plus 20 in the author's own series. From the literature only 20% of autopsies show active or possibly active stigmata of tuberculosis. From the necropsies personally studied as well as those afforded in the literature, Keil comes to the conclusion that the occurrence of tuberculosis in cases

of lupus erythematosus is only coincidental, and that there is no justification for the assumption that active tuberculosis is present merely because the patient has lupus erythematosus. No account is apparently taken in this study of the significance of allergic states.

**Sarcoid of Boeck.** This disease, the clinical manifestations of which range from papular eruptions to bluish tumors and infiltrations of the skin with a tuberculoid architecture, has long been the battle ground in the discussion of tuberculous etiology. The 1934 Strasbourg reunion<sup>19</sup> devoted practically its entire session to the consideration of this question. At the close, Pautrier surveyed the confused terminology, eliminating miliary lupoid from the conception of sarcoid, and likewise the deep subcutaneous sarcoid of Darier-Roussy. He pointed out that the sarcoid originally described by Boeck was a generalized disease affecting the skin, bones, glands and lungs and that in this conception, Schaumann's benign lymphogranulomatosis and the Besnier-Tennesson *lupus pernio* could be regarded as varieties of the same disease. Even Pautrier's attempt at terminologic reconciliation provoked disagreement, in which Darier considered that sarcoids presented a multiple etiology and Nicolas and Gaté did not believe that the deep sarcoid of Darier-Roussy could be decisively separated from the sarcoid of Boeck. Kissmeyer insisted on the resemblance of the condition to leprosy rather than tuberculosis; Schaumann supported the tuberculous etiology; and Ramel and W. Jadassohn spoke in favor of the tuberculous etiology. Hollander and Schlesinger<sup>20</sup> summarize the blood picture in 4 patients from the standpoint of a possible tuberculous etiology, with an inclination to classify the disease as tuberculous.

**Granuloma Annulare.** This condition has been one of the long-standing puzzles of dermatologic etiology. Michael<sup>21</sup> has produced a massive review of the literature of the etiology of *granuloma annulare*, from which he concludes (including the evidence from 8 cases of his own) that in some cases its tuberculous origin seems well supported, but that in a larger proportion it is not. In other words, it is still an infectious granuloma of unknown origin. Bertin,<sup>22</sup> at the Strasbourg reunion, draws essentially the same conclusions from his observations.

Michelson and Winer<sup>23</sup> pass some interesting comments on tuberculosis of the skin as it appears on the face. They emphasize the need for examining at least 25 sections from any biopsy for an adequate histologic appraisal, and frankly state that the histology of the various types of tuberculous lesions of the face is entirely inadequate for the drawing of sharp lines of differentiation. During the lymphocytic and exudative phase of the involution of individual lesions bacilli can frequently be found, but in the tuberculoid period they have been destroyed. Early lupus vulgaris is sometimes difficult to diagnose, for it looks more like a chronic diffuse inflammation. Central necrosis and caseation is not a necessity for the diagnosis and remnants of bloodvessels will usually be found at or near the center of the lesion. Most cutaneous tuberculosis may be looked on as arising from a hematogenously borne infection.

**Treatment of Cutaneous Tuberculosis.** From the very large literature on this topic, the account given by Funk<sup>24</sup> gives a particularly clear résumé of current conceptions. He estimates that there are 50,000 cases of cutaneous tuberculosis in Germany. Emphasis must be on the use in each individual case of every available constitutional measure in

addition to the complete destruction of the individual lesion. His estimate of the Sauerbruch-Hermannsdorfer-Gerson salt-poor diet is particularly interesting. He states that in from 6 to 24 months complete healing of lupus vulgaris can be secured by this dietary procedure, which he says surpasses even the Copenhagen light therapy in effectiveness. There are, however, diet refractory cases, and the necessity for following the prescribed dietary régime *exactly*, in amount, quality and character of food, makes it essentially an institutional procedure. The calorific requirements range from 2800 to 3000, with a protein-fat-carbohydrate ratio of 90 to 160 to 240. Its cost and the difficulties of preparation make it available to relatively few. In discussing light therapy, Funk emphasizes the caution necessary in cases of visceral involvement and stresses Rollier's plan of exposing the skin to air for some time before beginning the sun cure. The gradual exposure of increasing areas of the skin, the necessity for urinalyses, protection of head and eyes, and introduction of periodic rest periods for depigmentation are less familiar points. He speaks highly of tuberculin, emphasizing the necessity for watching possible visceral foci and commenting on the occasional extensive necroses with the sloughing out of an entire lesion, which occur under tuberculin therapy. He rates the bacillary preparations as worthless, including Friedman's vaccine. The technique which he employs is essentially that of Doutrelepon and Zieler, with a test dose of 0.01 to 0.1 mg. O T intradermally, increased to 0.25, 0.5 and 0.75 mg. intramuscularly. Hoffman begins with 0.002 to 0.5 mg., increasing very slowly. In discussing surgical excision, which he recommends as in the main the most satisfactory method for completely removing the cutaneous tuberculous focus, he recommends irradiation of the scar with ultraviolet light, under pressure, and the necessity for absolute and deep obliteration of the affected tissue, on account of the presence of small deep vascular foci. High frequency current is very satisfactory for excision purposes. Plastic restorations following surgical removals must be avoided except after years of satisfactory healing. The excision of a tuberculous area in the skin should not be attempted under local anesthesia, on account of the frequent unexpected necessity for deep excision. Pyrogallol and ointments are rated as suitable only to small lesions on the face and should always be combined with light therapy and the SHG diet. Funk commends the Pfannenstiel method of treating mucosal tuberculosis by the internal administration of sodium iodid with a gargle of hydrogen peroxid. Certain proprietary lipoiodin preparations can also be used in conjunction with the hydrogen peroxid, their effect presumably being to liberate nascent iodine in the tissues.

An equally valuable review of the treatment of lupus vulgaris from the Scandinavian standpoint is that of Lomholt.<sup>25</sup> The incidence of lupus vulgaris is rated by him as approximately 1 to 1000 in Denmark, and approximately the same in Germany. Direct inoculation is rare and produces only small and benign lesions. The extension may be from a suppurative lymphadenitis, a colliquative tuberculosis of the skin, especially in children, and from the region of tuberculous fistulae. Hematogenous and lymphogenous transplants from tuberculous foci in the lungs, lymph nodes and mucosa of the nose are rated as the most important. Patients with pulmonary tuberculosis seem fairly immune.

Lupus vulgaris is bovine in origin in 40% of cases, but there is no clinical difference in the course of the bovine and human type.

Eighty per cent of cures are obtained with Finsen light treatment with the concentrated carbon arc supplemented by carbon arc light baths. In early cases, with small lesions, the recovery is rated at 100%. The experience of the Finsen Institute with the Gerson diet in 40 patients, on whom it was used, was unsatisfactory, but a high vitamin diet was recommended. Like Funk, Lomholt recommends surgical excision as the most certain and successful method; with electrocoagulation, the risk of recurrence is less, but the scar more conspicuous. Scarification is rated as relatively ineffective; chemical corrosives including pyrogalllic acid remove most of the diseased tissue but rarely result in complete recoveries. The scar, moreover, is apt to undergo disfiguring hypertrophy, which also makes subsequent light treatment much more difficult. Treatment with the Kromayer water-cooled mercury vapor lamp is rated as less expensive but inferior to the Finsen light. The details of the Finsen method are fully given. Roentgen ray and radium are rated as giving a good transitory symptomatic effect, but definite cure is rare and Roentgen ray sequelæ common. In this connection, Hesse<sup>26</sup> attacks Roentgen ray as the most dangerous and unsatisfactory of all methods by arguments which are seemingly incontestable.

An interesting theoretical discussion of the mechanism of the SHG diet is that of Bommer.<sup>27</sup> He remarks that the disappearance of inflammation is characteristic of the SHG diet—the precise opposite of the tuberculin method of treatment and that the degree of healing under the diet depends on the degree of disappearance of the inflammation. He has observed benefit to skin injuries from Roentgen ray by placing patients on the SHG diet, the involution and paling of hypertrophic scars and recovery from an extensive vasomotor lividity in an individual case. From these observations he concludes that the effect of the SHG diet is on the vascular system and perhaps on the water balance of the body, and that the diet is, therefore, essentially a method of treating the vascular abnormality which underlies the tuberculous manifestations.

Tuberculin treatment of lupus vulgaris received strong support from the observations and experience of Aitken.<sup>28</sup> He cites particularly the work of the Edinburgh group, headed by Norman Walker, as a fairly conclusive demonstration of the great value of tuberculin therapy in treating lupus vulgaris. Spiethoff<sup>29</sup> briefly summarizes his technique of the treatment of lupus vulgaris with the Bucky Grenz irradiation, though he gives no precise statement of results. Large doses are necessary, the average being 4600 R with 9 kv., 2.5 cm. skin-window distance, and in some cases a dosage ranging as high as 6200 and 9200.

Areas larger than 3 cm. are not satisfactorily treated at a single exposure. In hypertrophic cases, a field of 2.5 cm. with 1 cm. skin-window distance and 28,750 R has been employed. The cost is less than Roentgen ray, the chief source of expense being damage to the windows of the apparatus. The method must be regarded as still unevaluated.

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(Titles have been omitted for sake of brevity.)

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 18, 1935

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**Observations on Adrenalectomized-depancreatized and Hypophysectomized-depancreatized Cats.** C. N. H. LONG and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). Adrenalectomized-depancreatized or hypophysectomized-depancreatized cats in the fasting state excrete less glucose and nitrogen than totally depancreatized animals. Furthermore, the intense ketonuria which is such a characteristic feature of depancreatized cats does not appear in the doubly operated animals and, in fact, is absent throughout the remainder of life unless measures are instituted that cause its appearance.

The survival of 15 adrenalectomized-depancreatized cats has been from 5 to 28 days while 8 hypophysectomized-depancreatized animals have survived from 18 to 85 days. The average survival of 16 depancreatized cats was around 4 days.

Removal of one adrenal and denervation of the other does not alter the diabetic condition in the cat. This suggests that the adrenal cortex rather than the medulla is responsible for the changes observed following total adrenalectomy. In addition the fact that hypophysectomy causes regressive changes in the adrenal cortex but not in the medulla is also evidence for this point of view.

The injection of anterior pituitary extract (Squibb) into hypophysectomized-depancreatized cats is followed by heavy ketonuria and if sufficient extract is given death in coma occurs in about 48 hours. The same extract when injected into a number of adrenalectomized-depancreatized cats does not produce ketonuria or coma even though amounts are administered in excess of those sufficient to kill the former group of animals.

The injection of large doses of epinephrin into animals of either type has been followed by ketonuria only once in each group. It was later found that the supposedly adrenalectomized cat had an accessory cortical nodule.

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**Experimental Studies in Gastric Physiology in Man. III. A Study of Pyloric Control—The Rôle of Milk and Cream in Normal Subjects and in Those with Quiescent Duodenal Ulcer.** G. GERSHN-COHEN and HARRY SHAY (Laboratories of Drs. Gershn-Cohen and Shay, Philadelphia). Roentgenologic studies were made in a group of 7 normal subjects and in another group of 4 with quiescent duodenal ulcer. The effects on gastric motility with meals of water, milk and cream were studied in both groups and attempts made to analyze and compare our results with the findings of others using different materials and methods. The effects of these substances on the various intrinsic factors in the mechanism controlling gastric evacuation were studied and compared with the effects of acids and alkalis on the control of the pylorus previously reported. Our findings reaffirm the known marked delay of gastric motility caused by the ingestion of milk and cream. The direct application of milk and cream to the duodenal mucosa through a duodenal tube produced a more pronounced delay in gastric evacuation than when taken by mouth. The most marked effects of these ingested materials were noted at the beginning of digestion and were characterized chiefly by spastic contraction of the pylorus with cessation of gastric peristalsis. When this effect was intensified by direct application of milk and cream through the duodenum, spasm of the duodenal cap and antrum occurred simultaneously, all three anatomic units acting as one. As digestion proceeded, spasm of the pylorus changed from a tonic to a clonic type, opening and closing of the pylorus becoming intermittent. Gastric peristalsis gradually returned to normal and intermittent filling and contraction of the duodenal cap followed. When both the duodenal cap and pylorus were opened simultaneously, gastric evacuation ensued so that motility from the stomach was intermittent. The subjects with quiescent duodenal ulcer differ from the normal only in that after disappearance of the initial pyloric and antral spasm, gastric peristalsis was intermittently markedly intensified rather than evenly vigorous. Emptying of water was quickest in the achlorhydric and hyperchlorhydric stomachs of the quiescent duodenal ulcer group, but emptying of milk and cream was lowest in the achlorhydric and quickest in the hyperchlorhydric.

An analysis of the elements of gastric evacuation would lead us to believe that the pylorus can and does function as a true sphincter; that an intestinal reflex, probably through the action of a humoral agent or chalone, is one of the principal controls in this action of the pylorus during digestion; that the intensity of reflex control of pyloric action is proportionate to the fat contents of milk and cream and the iodine number of the fats; and that the sphincteric action of the pylorus is the principal element governing gastric evacuation.

It appears that the tested substances act in controlling gastric motility principally through the reflex control of the action of the pylorus very much like strong acids and alkalis, the action being more intense and longer sustained.

Duodenal and gastric peristalsis are controlled by the same reflex mechanism as the pylorus, but are not so potent a motor element in gastric motility. They are, however, definite modifying factors. Whereas gastric tone, habitus of the patient, and posture during digestion might, under special conditions, have a bearing on gastric motility, gastric acid secretory response is a more constant modifying factor.

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**Changes in Bloodvessel Endothelium.** E. R. and E. L. CLARK (Laboratory of Anatomy, University of Pennsylvania. Illustrated by motion pictures with the assistance of E. A. SWENSON). The present studies on blood vascular endothelium were based upon microscopic observation of living bloodvessels and of the cells circulating through them, in the transparent tails of amphibian larvæ and in transparent chambers permanently installed in the ears of rabbits. In addition to prolonged observations in undisturbed vessels, the changes in blood vascular endothelium following mechanical injury and extravascular injections of minute quantities of various foreign substances (paraffin oil, carmine granules, lipid substances, protein, starch, and dilute croton oil) were studied in the amphibian larvæ, while, in the rabbit, observations were made upon the response of the vascular endothelium to heat, pressure and slight injuries.

In preceding descriptions of living bloodvessels, the lability of the vascular system in respect to its growth capacity was emphasized since it was shown that the formation of new capillary networks and the remodeling of the vascular pattern characteristic of embryonic growth and wound healing are processes which occur constantly in the adult mammal in response to minute mechanical, chemical and thermal stimuli. The present observations have demonstrated the lability of vascular endothelium in respect to its consistency. It was found that endothelium may undergo a series of changes in consistency depending on the character and strength of the stimulus as follows:

*Phase 1.* Usual condition of normal circulating bloodvessels in which the lining is smooth and blood cells of all kinds slip along without sticking. Tonicity and elasticity present, also active contractility in amphibian vessels. (No definite endothelial contractility has been observed in rabbit capillaries.)

*Phase 2.* Slight change in consistency of endothelium in response to mild external or internal stimuli. Leukocytes stick to walls momentarily. This change is usually transitory but may persist for hours or days with no leukocyte emigration. It may suddenly revert at any time



to Phase 1. No impairment in tonicity or elasticity—or contractility (Amphibia).

*Phase 3.* Endothelium becomes more sticky—leukocytes cling more tightly to walls, in larger numbers. No impairment of tonicity or elasticity. This phase may be transitory and revert rapidly to Phase 2 or 1.

*Phase 4.* Further change of endothelium to apparently softer consistency. Leukocytes emigrate through walls. This stage is usually transitory—reversal to Phase 3 or 2 usually takes place after a few hours and may occur so abruptly as to snare leukocytes in walls. No evidence of endothelial injury.

*Phase 5.* Further change in endothelium of vessels subjected to mechanical injury or located near toxic substance (croton oil, infection). Loss of tonicity and elasticity—vessels collapsed if empty, or distended and distorted if they contain blood. Extravasation of erythrocytes at localized places in weakened endothelium, but no actual break in wall. Resumption of circulation in vessels in this phase causes irregular bulgings. Recovery from this phase to Phase 1 takes an appreciable time (several days).

*Phase 6.* Serious injury to endothelium with break in continuity of vessel wall which separates into solid hyalin globules which are ingested by macrophages. Retraction of endothelium at two ends of such a break. No recovery from this phase. In succeeding days there may be new growth of capillary sprouts into such regions.

The rapidity with which changes in endothelial consistency may take place, and the relatively minute stimuli necessary to elicit the preliminary changes, together with their reversibility are of undoubted importance for an understanding of the physiological activity of blood-vessels.

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ORIGINAL ARTICLES.

CLINICAL ESTIMATION AND SIGNIFICANCE OF CALCIUM-ION  
CONCENTRATIONS IN THE BLOOD.\*†

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ONE of the so-called physiologic constants is the concentration of calcium in the blood plasma.‡ That the maintenance of this concentration within a relatively narrow normal range is a function of the parathyroid glands has been clearly shown by the work of Collip.<sup>1</sup> This range is, on the average, between 10 and 11 mg. per 100 cc. for man, beef, sheep, dogs, cats and rats and somewhat higher for rabbits and guinea pigs.<sup>2</sup> For man, in individuals, the extremes of the normal range may be considered to be 9 and 11.5 mg. per 100 cc.<sup>3</sup>

Owing to a considerable interest in the behavior of calcium in the body in health and disease, the gross changes in the concentration of calcium in the serum, occurring in various clinical conditions, have received a great deal of attention. The more important find-

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† This work was aided by a grant from the Josiah Macy, Jr., Foundation.

‡ While the majority of observations reported in this paper were made upon serum from coagulated blood, it has been shown that the results upon serum and upon plasma from blood prevented from coagulation, by a means which does not interfere with the ionization of calcium, are indistinguishable.

ings, with reference to which agreement is more or less general, are summarized in Table 1.

TABLE 1.—TOTAL CALCIUM IN PLASMA OR SERUM.

<i>Elevated</i> (12 to 16 mg. per 100 cc.).
Hyperparathyroidism.
Hyperproteinemia (especially multiple myeloma).
Overdosage of viosterol.
<i>Within or near the normal range</i> (9 to 11.5 mg. per 100 cc.).
Rickets.
Osteomalacia.
Paget's disease.
Senile osteoporosis.
Calcinosis universalis.
Tetany of alkalosis.
<i>Lowered</i> (4 to 8.5 mg. per 100 cc.).
Hypoparathyroidism, including parathyroid tetany.
Hypoproteinemia.
Hyperphosphatemia of nephritis and uremia.
Some cases of rickets and of osteomalacia.
Infantile tetany.

In 1913, Rona and Takahashi<sup>4</sup> first demonstrated that the calcium in the serum could be differentiated into two fractions, about 50% being capable of passing through a membrane impermeable to proteins, the remaining 50% remaining with the proteins of the serum. These fractions have since come to be known as diffusible and non-diffusible. They concluded that the non-diffusible fraction is bound in some way to protein, and this conclusion has been almost universally accepted. Interest has, however, centered upon the state of the diffusible calcium, known to be free in solution. Nor is this merely an academic interest, since it appears that the physiologic activity and hence the clinical importance of the calcium in the blood depend upon its physical-chemical state.

In the light of modern chemical theory the common salts of calcium in dilute aqueous solution are to be thought of as completely dissociated into calcium ions, each carrying a double positive electrical charge, and the corresponding negatively charged ions. Calcium chlorid, for example, does not exist as such in dilute solution, but each molecule dissociates into one calcium ion ( $\text{Ca}^{++}$ ) and two chlorid ions ( $\text{Cl}^-$ ). On the other hand, certain chemical substances, such as citrate, are capable of binding calcium in complex combinations, in such a way that it loses its electrical charges, certain of its chemical properties and at least certain of its physiologic activities.<sup>5</sup> Since  $\text{Ca}^{++}$  and calcium bound to such substances as citrate both pass freely through semipermeable membranes, diffusion methods are not of use in distinguishing between these forms.

Starting with general agreement that at least part of the diffusible calcium in serum is in the form of free  $\text{Ca}^{++}$ , and with much reason to believe that this form is of primary physiologic importance, two schools of thought, both supported by experimental evidence, have developed with reference to the state of the diffusible calcium of

the blood. One school has held that all, or very nearly all, of the calcium not bound to protein is ionized (Fig. 1, *A*). The other school, relying chiefly upon what is known concerning the solubility of calcium carbonate and calcium phosphate, has held that of approximately 5 mg. per 100 cc. of serum of the calcium not bound to protein, not more than 2 mg. can be in the ionized state. In order to account for the remaining 3 mg. a diffusible form of calcium, bound to some citrate-like substance, as yet unidentified, has been postulated, and has sometimes been called calcium-X (Fig. 1, *B*). As to cerebrospinal fluid, which contains only minute amounts of protein, and a total of about 5 mg. of calcium per 100 cc., all diffusible, the same question arises, and the same differences of opinion have existed. Although Greenberg and Greenberg<sup>6</sup> have recently concluded that there is no direct evidence in favor of it, most recent reviews<sup>2,3,7,8,9</sup> incline toward acceptance of the calcium-X hypothesis. Present thought concerning the state of calcium in the serum is summarized in Fig. 1.

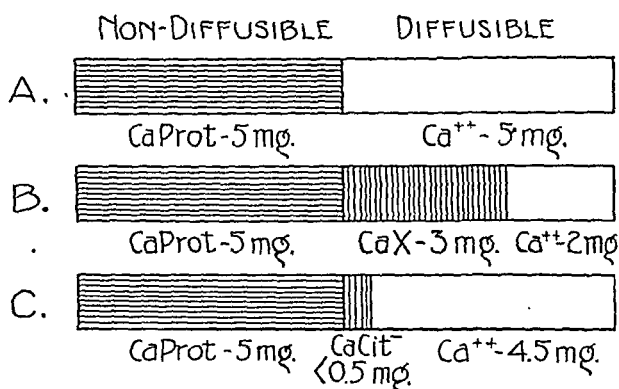


FIG. 1.—Various views of approximate distribution of calcium in normal human serum. C represents the findings reported in this paper.  $\text{Ca}^{++}$ , ionized calcium; CaProt, calcium bound to protein; CaX, hypothetical bound but diffusible calcium;  $\text{CaCit}^-$ , calcium bound to citrate.

In view of the uncertainty as to the conditions present in the fluids of the normal body it is not surprising that interpretation of abnormal findings has been a source of great difficulty, and of further difference of opinion. To the clinician this has meant (1) that a normal figure for the total calcium of the serum might possibly conceal an abnormal distribution between the various forms, and (2) that no sound basis has existed for clinical interpretation of abnormal fluctuations in the total calcium level.

Obviously the key to these difficulties lies in the possibility of making direct observations of  $\text{Ca}^{++}$  concentrations. Attempts to find a suitable method, by electrometric and other means, have not been lacking, but have not met with success, particularly when applied to biologic fluids. The studies here reported originated

from an attempt on the part of the authors to make a new approach to such measurements.

The method finally adopted took advantage of a familiar biologic preparation, the isolated heart of the frog, already known to be extremely sensitive, within a certain range, to changes in the calcium content of its nutrient fluid. As to the method, it was necessary to show that this sensitivity could be reduced to quantitative terms, that the preparation is adapted to biologic fluids from other species and that the sensitivity is specific for calcium in the ionized form, the preparation being indifferent to calcium bound in combination with other substances. These conditions were met, and a method which is workable and reasonably accurate resulted.<sup>10</sup> It is not recommended for use in the clinical laboratory, but the studies which it made possible have yielded another method of estimation of  $\text{Ca}^{++}$  concentrations, to be described, which is available for routine clinical use.

Observations by the frog heart method quickly disposed of the question of the state of calcium in the fluids of the normal human body. The  $\text{Ca}^{++}$  concentration in normal human fluids was found to be in the neighborhood of 5 mg. per 100 cc. of fluid, and this was found to be true whether cerebrospinal fluid, containing a total of 5 mg. of calcium per 100 cc., or serum, containing twice this amount, was examined. It thus appears that all or nearly all of the calcium in protein-free fluids, such as cerebrospinal fluid, is present in ionized form, and that in protein-containing fluids, such as serum, plasma, pleural fluid, and ascitic fluid,  $\text{Ca}^{++}$  and calcium bound to protein are together sufficient to account for all or almost all of the total calcium. There thus seems to be no further reason to postulate quantitatively significant amounts of a third form of calcium in the fluids of the normal human body, although it can scarcely be doubted that a small but insignificant amount of bound but diffusible calcium, corresponding to the small amounts of citrate present in human fluids, does exist in these fluids (Fig. 1, C).

The calcium-protein relationship was next investigated, and this study led to the discovery that the ionization of calcium, in protein-containing fluids, is determined by a chemical equilibrium between calcium and protein, and that this equilibrium can be described as a first approximation by a simple equation. The hydrogen-ion concentration also plays a part in this equilibrium, as do magnesium, citrate and the albumin to globulin ratio, but the influence of these factors, individually and collectively, is small. For the details of these relationships reference is made to a previous paper by the authors.<sup>11</sup>

Having shown that the distribution of calcium between  $\text{Ca}^{++}$  and calcium bound to protein depends upon the total protein present, it now became possible to calculate  $\text{Ca}^{++}$  concentrations from values for total calcium and total protein. Studies, some of which are

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## FAILURE TO FIND PRESSOR AND ANTIDIURETIC SUBSTANCES IN PATIENTS WITH TOXEMIA OF PREGNANCY.

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IN 1931 Anselmino and Hoffman<sup>1</sup> reported evidence of the presence of a blood pressure raising and antidiuretic substance in the blood of patients with eclampsia and "nephropathie." They define "nephropathies" as "those patients who have hypertension, edema, albuminuria, and so forth, but who differ from those with eclampsia by the normal galvanic nerve-muscle response and by the absence of convulsions. Apparently this corresponds to our preëclamptic toxemia. This substance they believed closely allied to pituitrin because of similar behavior chemically (both substances are destroyed by alkali and ultraviolet light, and adsorbed on talcum) and because of the ability of the pituitrin to reproduce some of the features of eclampsia, such as convulsions and coma, increased blood pressure, hemoglobinuria and capillary spasm.

They used rabbits in their experiments. After having 90 cc. of water put into their stomachs with a stomach tube, these rabbits were injected subcutaneously with protein-free ultrafiltrates of serum from eclamptics and "nephropathies." A definite and marked inhibition of the normal diuretic response was noted. In other rabbits they observed a rise in the blood pressure of the carotid artery after injections of the ultrafiltrate from those patients with blood pressures over 180 mm. of mercury.

These findings seemed of the utmost importance in relation to the etiology and treatment of eclampsia and an attempt was made to repeat this work.

**Methods.** The methods described by Anselmino and Hoffman were followed, except those for the preparation of the collodion membranes with which to make the ultrafiltration and for the recording of the blood pressure. As many factors affect the permeability of collodion membranes, and we could not be certain of reproducing their membranes from the data given, a graded series of carefully standardized membranes was made with the technique of Dr. Edward Cohn.<sup>2</sup> As their purpose in filtering was simply to remove the serum proteins, a sac was used, the permeability of which was just sufficient to hold back the proteins. This was made with 3% collodion (made from dried DuPont's nitrocellulose, viscosity 43 seconds) in 25% anhydrous ether and 75% absolute alcohol. The glass mold was rotated 8 times a minute with an electric motor and the collodion applied at an even rate from a separating funnel. Four reënforcing coats were applied at top and bottom at 5-minute intervals and then 4 filtering coats at 3-minute intervals. Ten minutes after the last coat, the sac was placed in 95% alcohol for 30 minutes and then in distilled water until used. A new sac was used for each serum. It was mounted in a suction apparatus made by MacAlaster-Bicknell of Cambridge and filtration carried out at a negative pressure of 150 mm. of mercury. This was obtained with a water pump and a mercury valve. After the preliminary work the graded series was obtained by varying only the time between coats. The series was checked at intervals to be sure that the sac used gave the desired permeability. The sac used, as well as a much less permeable membrane in the series, was shown to allow easy passage of pituitrin mixed with acidified plasma.

To determine the blood pressure effects rabbits were lightly anesthetized with ether, an incision made in the neck and a section of the carotid artery brought outside of the skin. At least 6 hours were allowed for recovery and a new rabbit was used for each experiment. At the time of the experiment the carotid artery was cannulated under local cocain anesthesia and the blood pressure recorded on a kymograph with a mercury manometer. A control record of 30 minutes to an hour was taken to show the normal variations and the effect of slight manipulation of the animal. Thus a continuous written record was obtained which was thought to be more reliable than any type of intermittent reading of pressure.

One hundred cubic centimeters of blood were obtained from the patient and 5 cc. of 5% sodium citrate were added; 50 cc. of plasma were removed and acidified by the addition of 2.5 cc. 1 N. acetic acid. It was then put into the collodion sac and suction started. The ultrafiltrate was always clear, colorless and albumin-free by biuret and nitric acid tests. In some instances it was stored in the icebox overnight. Immediately before using, it was neutralized with 1 N. sodium hydroxid to pH 7, using a spot plate and bromthymol blue as an indicator.

For the antidiuretic experiments only rabbits were used which had relatively consistent diuresis curves after receiving 90 cc. of water by stomach tube and 10 cc. of saline subcutaneously. They were kept without food or water from 12 to 15 hours before the experiment. Over half of the rabbits had to be discarded because of inconsistent diuresis curves, and of the remainder 3 well controlled rabbits were used for the majority of the experiments. There was some variation in the height of the diuresis even in these rabbits, but there was always a striking difference after the injection of small amounts of pituitrin or pitressin. The results obtained with one of these rabbits are shown in Table 1. Of the ultrafiltrate, 10 cc. were

injected subcutaneously in the experiments, while the controls were given 10 cc. of saline. All saline given subcutaneously was 0.85% sodium chlorid which had been neutralized with 1 N. sodium hydroxid after the addition of 5 cc. of 1 N. acetic acid per 100 cc. of saline.

**Case Abstracts. Patients with Toxemia.** CASE 1.—Mrs. M. B., aged 34, Para VI. Previous deliveries normal. Well during this pregnancy until 3 weeks ago when feet and hands began to swell. No other symptoms.

*Physical examination* negative except for slight pitting edema of lower legs. Eight months pregnant. Blood pressure, 194/100. Albumin—large trace with numerous hyalin and granular casts. N. P. N., 25. Patient was kept for 3 weeks during which time blood pressure was 140/90–100. Urine showed large trace of albumin. Membranes ruptured 2 weeks after entry and patient had a normal delivery of a normal baby. Just before delivery blood pressure was 160/110. Patient had a normal convalescence with the blood pressure going down to 110/80 and a very slight trace of albumin with no casts. Blood taken 2 days after entry when blood pressure was 194/120.

*Diagnosis.* Preëclamptic toxemia.

*Experimental Observations.* No antidiuretic response. No pressor response.

CASE 2.—Mrs. K. M., aged 36, primipara, due April 4, 1933. Sent in March 25, 1933, by local physician because of increased blood pressure and albuminuria for 1 week. Patient had felt entirely well until March 15 when feet and hands became swollen. Blood pressure on entry was 196/130 and urine showed a trace of albumin. *Past history* negative. Blood pressure normal in early pregnancy. *Physical examination:* Obese, hirsute woman with marked edema of both legs, moderate edema of hands, face and sacrum. A few râles noted at both bases. Blood pressure varied between 170–190/100–110 for the first 4 days. Blood was taken on third day for pressor and antidiuretic effect. On the fourth day a baby, 8 pounds, 11 ounces, was delivered by Cesarean section. Urine showed a large trace of albumin on entry. After section blood pressure gradually came down to 130 and the albumin decreased. When seen 6 months later blood pressure was 120/72. No albumin present. Patient felt perfectly well.

*Diagnosis.* Preëclamptic toxemia.

*Experimental Observations.* No pressor effect.

CASE 3. Mrs. C. C., aged 38, old primipara due February 17 and sent in February 1, 1933, because of high blood pressure and albuminuria.

For the past 3 months patient had had increasing edema of the ankles, headache for 1 month, vomiting off and on for 1 month, and blurred vision of the right eye for 1 week.

On entry, patient had marked edema of the hands and slight edema of face. Blood pressure was 220/164. Albumin—trace to large trace with many hyalin casts and a few granular casts. For 2 days blood pressure remained 210/98–120 and then a classical Cesarean section was done under spinal anesthesia. Blood for determination of pressor and antidiuretic substance was taken on day of operation. After operation the blood pressure gradually came down to 130/88 and the urine showed a slight possible trace of albumin. The baby did well. Since delivery, patient has shown no albumin and the blood pressure has been 126–134/84.

*Diagnosis.* Preëclamptic toxemia.

*Experimental Observations.* No antidiuretic response. No pressor response.

CASE 4.—Mrs. G. A., aged 27, Para IV, due August, 1933, was referred on June 26 from district for swelling of hands, face and feet, and hypertension. Blood pressure, 184/108, and large trace of albumin. Blood pressure continued at 190/100 and albumin showed a trace for 10 days



when she went into labor and delivered normally a stillborn infant. After delivery blood pressure fell to 120/80 and albumin disappeared. Blood was taken the day after entry.

*Diagnosis.* Preëclamptic toxemia.

*Experimental Observations.* No antidiuretic response. No pressor response.

CASE 5.—Mrs. A. F., aged 32, Para IV, due May 27, 1933. Patient entered May 28, 1933, because of acute pulmonary edema. On admission was markedly dyspneic; blood pressure was 195/100; pulse, 120. She had a presystolic murmur. Lungs were full of râles. Patient given morphin during the night. Blood taken for pressor antidiuretic response that night. The next day patient went into labor and delivered a normal infant. After delivery blood pressure went down gradually to 150/100, where it remained for a week then went down to 120/70. Urine showed a trace of albumin on entry and for first few days. Since discharge patient has had no albumin, no elevation of blood pressure and no dyspnea.

*Diagnosis.* Preëclamptic toxemia, rheumatic heart disease, mitral stenosis.

*Experimental Observations.* No pressor effect.

CASE 6.—Mrs. V. G., aged 41, para VII, due May, 1933. Referred on May 27, 1933, with blurred vision, headaches of 2 months' duration, edema of legs for 2 months. Blood pressure was 190/120 and eyegrounds showed many large and small areas of cotton-wool exudate and many small hemorrhages in the retina. Blood pressure remained 180-190/120. Membranes were ruptured on May 29 and patient went into labor and delivered a stillborn infant full of congenital abnormalities. Placenta was normal. After delivery, blood pressure was 170/110; albumin, negative; fundi unchanged. When seen 6 weeks later blood pressure was 160/96; albumin, negative.

*Diagnosis.* Toxemia, superimposed upon underlying hypertension.

*Experimental Observations.* No pressor effect.

CASE 7.—Mrs. C. C., aged 22, primipara, due April 10, 1933. Patient sent in February 25, 1933 because of edema of ankles, headaches, of 1 week's duration. On entry blood pressure was 160/98; albumin, trace; marked edema of legs. On February 28, 1933, blood taken for pressor-antidiuretic test. Blood pressure was 164/94 at that time. Albumin and hypertension continued 1 week, then gradually decreased. On March 7 patient discharged with normal blood pressure and no albumin. Seen again March 31. Blood pressure was 150/100 and a large trace of albumin was present. On April 2 patient entered in active labor, delivered normally of a baby, 6 pounds, 6 ounces. Blood pressure and albumin decreased to normal after delivery.

*Diagnosis.* Preëclamptic toxemia.

*Experimental Observations.* No antidiuretic response. No pressor effect.

CASE 8.—Mrs. A. C., aged 36, old primipara, entered the hospital on May 17, 1933, 2 weeks from term, with a history of a convulsion 2½ hours before admission, vomiting, incoördinated movements and coma. Apparently perfectly well until 9 A.M. of day of admission when she complained of nausea, vomiting and epigastric pain. At 5 P.M. patient had a convulsion and was brought into the hospital.

On entry, patient was found to be an obese Italian woman, semicomatose, vomiting dark yellowish material. Incoördinated movements continued. Edema of ankles present. Blood pressure 124/80. Eye grounds showed fair sized nerve fiber layer hemorrhage below left disk, retinal veins distended and moderate retinal sclerosis. Urine showed large trace of albumin, and was loaded with red and white blood cells and casts. N. P. N., 35. Blood pressure varied between 130-180/90-100 for first 2 to 3 days after admission. Membranes then ruptured and an edematous stillborn was

delivered. Patient constantly improved after delivery and on postpartum visit had a normal blood pressure. No albumin present. Blood was taken on night of admission.

*Diagnosis.* Eclampsia.

*Experimental Observations.* No antidiuretic response.

*Patients With Antecedent Hypertension, Vascular Changes, Chronic Nephritis.*

CASE 9.—Mrs. G. N., aged 43, Para III, sent in at term because of hypertension.

*Past history* negative. Patient felt entirely well during this pregnancy. Had edema of both ankles for 4 months, swelling of hands for 2 or 3 months, face for 1 month. Patient did not go to a doctor until just before entry when blood pressure was found elevated and she was sent into the hospital.

On entry, legs were markedly edematous, also sacrum. Fingers and face moderately swollen. Two and a half days after entry 100 cc. of blood taken. Blood pressure, 200/126. Urine showed a large trace of albumin with many hyalin and fine granular casts. Patient went into labor soon after and had a normal delivery of a healthy baby. Since delivery patient has continued with her hypertension but has had no albumin and has had signs and symptoms of mild heart failure.

*Diagnosis.* Vascular hypertension.

*Experimental Observations.* No antidiuretic response. No pressor effect.

CASE 10.—Mrs. G. M., aged 32, Para V, due March 26. Entered hospital March 8, sent in because of hypertension. Blood pressure, 195/115 and urine showed trace of albumin.

On entry, patient had fluid at both bases. With rest in bed patient lost weight but blood pressure remained at 170/120 and she continued to show a trace of albumin. Three days after entry patient delivered a stillborn baby. N. P. N., 40. Blood for analysis taken on day after admission, on which day blood pressure had been 180/120. After delivery, patient had 2 attacks of nocturnal dyspnea and was transferred to another hospital for treatment. Blood pressure continued elevated 150/100 during remainder of hospitalization.

*Diagnosis.* Vascular hypertension plus cardiac decompensation (possible superimposed toxemia).

*Experimental Observations.* No antidiuretic response. No pressor effect.

CASE 11.—Mrs. O. D., aged 33, Para VII, due May 29. Patient sent in March 22, 1933, because of hypertension on her first visit. Obstetric history negative until 1927 when she had high blood pressure at end of fourth pregnancy. In 1929 had elevated blood pressure with fifth pregnancy but no albumin. In 1932 patient had a macerated fetus. Blood pressure readings not obtained after deliveries. She had felt perfectly well this pregnancy. Blood pressure, 230/130. Albumin, none. Patient had no edema. Uterus was the size of a 5 months' pregnancy. Eyegrounds showed slight to moderate sclerosis of retinal arteries. On March 27 patient went into labor and delivered a 6 $\frac{3}{4}$  months' macerated fetus. After delivery, blood pressure remained at 200/90–130. Urine negative for albumin. Patient has not been seen since discharge.

*Diagnosis.* Vascular hypertension.

*Experimental Observations.* No antidiuretic response. No pressor effect.

*Non-pregnant Hypertensives.*

CASE 12.—Mrs. A. C., aged 43, Para V, entered the hospital on July 30, 1932, when 2 months pregnant with a blood pressure of 240/136. Urine showed no albumin. Patient had an elevated blood pressure since her second pregnancy 10 years ago. Patient complained of headache and spots

before the eyes of 1 month's duration, also of increased drowsiness and irritability for 4 to 6 weeks. Physical examination negative except for sclerosis of retinal arteries. Very slight trace of albumin. N. P. N., 48. On August 8 a hysterectomy was performed. Following operation blood pressure was 180-210/120-140. In the postpartum clinic blood pressure was 208/140, 230/150. On March 13, 1933, 6 months after operation, patient had a urea clearance test, at which time blood was taken to test for pressor anti-diuretic effect. Blood pressure at this time, 230/150. Urea clearance test was normal (108%).

*Diagnosis.* Non-pregnant hypertensive.

*Experimental Observations.* No antidiuretic response. No pressor effect.

CASE 13.—Mr. S. K., aged 57, entered the hospital March 8, 1933, because of pains in the legs for 2 months. He had had hypertension for several years. His heart was enlarged to the left. Blood pressure was 245/130. Urine, negative. Blood taken for pressor-antidiuretic test on March 10, 1933.

*Diagnosis.* Hypertension, chronic myocarditis, arteriosclerosis.

*Experimental Observations.* No pressor effect. No antidiuretic response.

CASE 14.—Mr. H. L., aged 56, janitor, entered the hospital because of nocturia, headache, blurring of vision, of 15 years' duration. Patient had marked thickening of peripheral arteries. Blood pressure, 230/130. Eye-grounds showed both nerves markedly blurred in outline. Several hemorrhages and considerable exudate in both retinae. Heart enlarged transversely. Blood pressure over 220 during hospital admission.

*Diagnosis.* Hypertension, arteriosclerosis, chronic myocarditis.

*Experimental Observations.* No pressor effect.

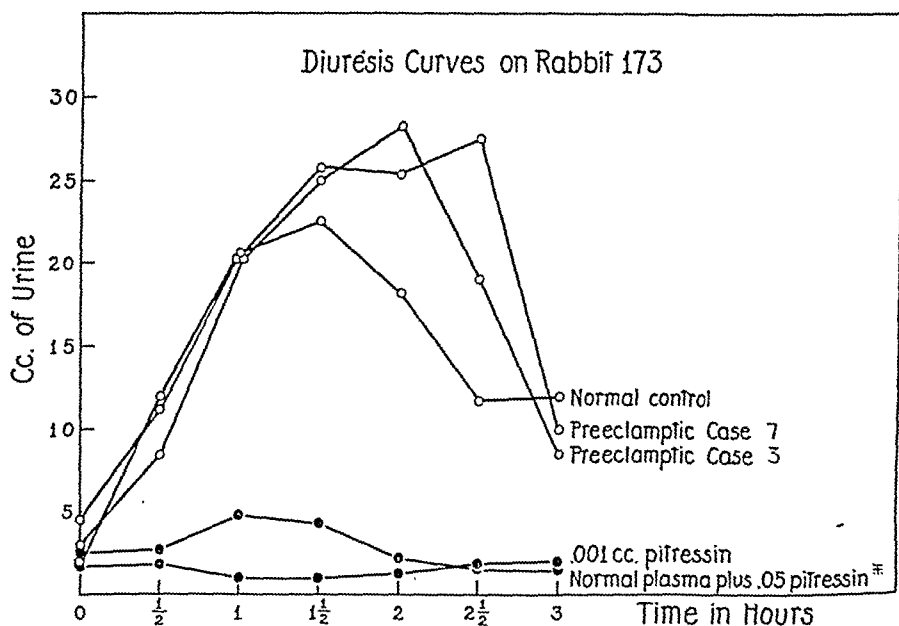


FIG. 1

**Results.** Blood was obtained from 1 eclamptic, 7 preeclamptics, 3 pregnant women with hypertension and chronic nephritis, and 3 non-pregnant patients with hypertension.

*Antidiuresis.* Figure 1 gives the diuresis curves in the rabbit (No. 173) after receiving 90 cc. of water by stomach tube in each

instance and 10 cc. subcutaneously of saline, pitressin in saline, ultrafiltrate of normal acidified plasma plus pitressin, or ultrafiltrate from blood of patient with toxemia. None of the ultrafiltrates caused any inhibition of diuresis while 0.001 cc. of pitressin was adequate to cause a definite and lasting antidiuresis. Similar results were obtained with the other filtrates. Nor could a consistent change in the sodium chlorid concentration be demonstrated.

TABLE 1.—DIURESIS CURVES ON ONE RABBIT, No. 173 (Cc. OF URINE).

Date.	Control, ½ hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	2½ hrs.	3 hrs.	Injected 10 cc. of
12/6/32	0.0	7.7	6.2	14.8	10.8	10.8	12.0	Saline.
12/8	2.3	5.6	13.5	14.9	18.0	16.8	11.0	Saline.
12/10	2.0	12.0	20.6	22.5	18.2	11.7	12.0	Saline.
12/12	2.0	2.7	2.8	2.0	1.0	0.8	1.6	0.01 Pitressin.
12/14	2.4	6.0	16.3	21.2	18.6	18.8	19.2	Saline.
12/16	1.8	1.8	0.9	1.0	1.3	1.9	2.0	0.001 Pitressin.
12/24	3.0	1.8	13.5	20.2	22.0	9.1	....	Saline.
1/ 3/33	1.0	3.0	7.8	13.9	12.8	17.0	13.2	Saline.
1/23	2.0	6.0	13.0	20.0	11.8	13.4	....	Saline.
2/ 4	2.5	2.7	4.8	9.5	14.0	17.6	17.4	Case 8.
2/14	2.6	1.7	1.8	4.4	2.2	1.6	1.6	0.01 Pitressin.
2/15	2.0	2.6	6.3	13.3	32.2	30.4	24.2	Saline.
3/1	3.0	8.5	20.8	25.8	25.4	27.5	10.0	Case 7.
3/3	1.0	1.0	10.0	25.0	30.0	23.5	11.5	Saline.
3/7	1.8	11.2	20.5	25.0	28.2	19.0	8.5	Case 3.
3/11	2.5	2.5	12.4	22.0	17.5	22.4	13.0	Case 2.
3/16	2.1	....	30.0	28.2	36.7	16.5	8.0	Case 9.
3/21	1.5	1.8	12.2	22.7	18.7	9.2	....	Case 11
4/23	2.2	1.0	14.4	25.0	20.5	18.5	....	Case 10
4/25	3.0	6.0	30.0	26.0	32.0	28.0	23.5	Saline.
5/18	2.0	10.5	27.0	34.0	32.0	9.0	3.5	Case 12
6/28	1.5	17.5	21.7	29.0	26.3	24.5	13.8	Case 4.
7/6	2.4	0.0	5.2	14.6	22.4	15.0	12.0	Case 1.

**Pressor Effect.** No pressor response was observed after the injection of any of the ultrafiltrates, while small doses of pitressin (0.01 cc.) intravenously caused a slight rise in blood pressure and then a fall followed by a return to normal. Larger doses of pitressin (0.02 cc.) caused a more marked fall after the slight rise. Even after prolonged observation of the blood pressure there was no rise at all after the injection of the ultrafiltrates either subcutaneously or intravenously.

**Conclusions.** Neither blood pressure raising nor antidiuretic substances were found in the blood of 14 patients classified as non-pregnant hypertensive (chronic nephritic) toxemia, preëclamptic toxemia, and eclampsia.

**NOTE.**—Since this paper was written an article has appeared by Byrom and Wilson (Quart. J. Med., 3, 361, 1934) also failing to find antidiuretic substances in the blood of patients with preëclamptic toxemia and eclampsia.

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# THE HISTOPATHOLOGY OF THE HEMOPOIETIC TISSUES IN HEMOPHILIA.

## AN UNEXPLORED FIELD.\*

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NECROPSIES on cases of hemophilia have been strangely infrequent in recent times, and of those in the literature concern has been chiefly with the hemorrhage found, the secondary degenerations and necroses and the condition of the vessel walls, rather than with the state of the hemopoietic tissues, an omission which seems particularly odd in view of the usual belief that the blood platelets are at fault in this disease. Since Neumann first connected the bone marrow with hemopoiesis (1868), we have not been able to find a single published necropsy on a case of hemophilia that has included a study of the hemopoietic tissues. The unusual circumstance, then, of having 3 cases of hemophilia come to necropsy within a short period, has led us to study the postmortem picture in the hope that further light might be thrown on the nature of the disease and in the belief that, in any case, published studies by modern methods would be of service. The 3 cases were the more valuable for the purpose in that, as seen below, one died as the direct result of hemorrhage, another of a combination of infection and hemorrhage and the third of infection without any relation to hemorrhage, thus constituting three variants of a natural experiment, the subjects being of approximately the same age.

Of particular interest was the bone marrow cytology, which is therefore presented in detail, especially that of the megakaryocytes, which are generally regarded as the originators of the blood platelets and directly concerned with blood coagulation, the major disturbance in hemophilia.

Abstracts of the clinical and postmortem findings follow:

**Case Abstracts.** CASE 1.—An Italian boy (F. P.), aged 11, was admitted to the Philadelphia General Hospital February 5, 1935 (service of Dr. Eliason; attending, Dr. Ferguson), having fallen on January 30, 1935. He complained of pain in back on February 2, limped with the right leg and

\* This is regarded as No. V in the series of "Studies on the Structure and Function of Bone Marrow," this general title being subordinated that the main subject might not be overlooked.

ultimately was confined to bed with intense abdominal pain in lower right quadrant. He vomited twice on February 3. *Past History*: First hemophilic tendency appeared at 7 months, with prolonged hemorrhage following incision of gums to aid teething. Minor lacerations bled for days, requiring hospitalization on many occasions. He had had several "rheumatic attacks" and, on previous admission, murmurs were heard over mitral and tricuspid areas. *Family History*: Possibly the first generation of hemophilia (little information available concerning relatives in Italy); a brother, aged 7, shows bleeding time of 2 minutes and coagulation time of 24 minutes; a nephew, age 20 months, shows bleeding time of 2 minutes and coagulation time of 15 minutes, each having shown hemophilic signs and symptoms since infancy. A control test on a healthy person gave a bleeding time 1 minute and coagulation time 4 minutes. *Physical Examination*: Acutely ill child in severe pain, with right thigh flexed on abdomen; head and neck normal except for coryza and tonsillar hypertrophy; lungs present vague impairment at right apex, friction rub at right base, fine basal and inter-scapular râles; heart normal except for tachycardia; right lower quadrant of abdomen extremely tender and rigid with a palpable mass (hemorrhagic? inflammatory?); marked rectal tenderness; extremities normal except for abnormal flexion of right leg (enlarged knee joints on previous admission). *Laboratory Tests*: Urine shows trace of albumin and occasional leukocytes; erythrocytes 4,120,000 to 4,130,000; leukocytes 17,150 to 20,800; neutrophils 72% (myelocytes, 0; juv., 0; stab, 40; segmented, 32), lymphocytes 26%, monocytes 2%; coagulation time, 35 minutes; bleeding time, 3 minutes; electrocardiogram, normal; tuberculin test doubtfully positive. *Course*: February 5, 1935, exploratory laparotomy showed extensive retroperitoneal hemorrhage; no intraperitoneal lesion found (Bovie knife used and no operative hemorrhage incurred). February 6, abdomen tense and tender; rising temperature, pulse and respiration; February 7, death. *Final diagnosis*: Hemophilia with massive extraperitoneal hemorrhage. *Necropsy* (P. G. H., 28846, 7 hours after death, Dr. R. W. Mathews). Well-developed male, height 132 cm., weight 24.5 kg., with recent surgical incision in right lower abdominal quadrant; no external evidence of hemorrhage. On opening abdomen an extraperitoneal hematoma is encountered of 2 to 4 cm. thickness, covering entire right lower quadrant, the medial half of left lower quadrant and laterally over entire right flank, extending from diaphragm over right psoas along the intermuscular fascial planes well into right thigh. There is intrapsoas hemorrhage with muscular necrosis. *Aorta* is smooth, elastic and of normal caliber. *Heart* weighs 140 gm. (left ventricle, 1.3 cm.; right ventricle, 4 cm.; aortic valve, 4.5 cm.; mitral, 8 cm.; tricuspid, 9 cm.; pulmonary, 5.5 cm.), being slightly enlarged; pericardium at apex thick, gray and shaggy; myocardium firm and pale red-gray; auricular endocardium slightly thickened; aortic leaflets uniformly thickened but functionally competent; free edges of mitral leaflets thickened and rolled and chordæ tendineæ shortened and thickened, papillary muscles being hypertrophied and shortened; coronary vessels apparently normal. *Lungs* present glistening pink-gray pleuræ, left weighing 140 gm., right 180; parenchyma soft, tough and inelastic; crepitant throughout; tracheobronchial tree congested and contains blood-tinged mucoid exudate. *Spleen* weighs 80 gm. and measures 9 by 6.5 by 3 cm., capsule being smooth, gray and glistening; parenchyma gray-red, firm and resilient, follicles visible as gray dots. *Lymph nodes* appear normal. *Kidneys* show variation in size, left weighing 60 gm. and measuring 7 by 4 by 2 cm.; right 100 gm., 11.5 by 4 by 3 cm.; each being of normal shape; capsules thin, strip with ease leaving smooth, pale brown surfaces; cut edge slightly rolled and blood oozes from cut surface; general architecture normal. Lower urinary tract and genitalia show no lesions. *Gastro-intestinal tract* including appendix

appears quite normal. *Liver* weighs 800 gm. and measures 15 by 8.5 by 5 cm., presenting a thin capsule and fairly firm red-brown parenchyma that retains normal lobular architecture; blood oozes from cut surface; gall bladder and bile ducts appear normal. *Pancreas* firm, gray-pink and apparently normal. *Adrenals* show yellow cortices and dark brown medullæ. *Skeleton* appears normal, bone marrow being dark red (vertebra, sternum, rib and femur). *HISTOLOGY.* *Heart* shows slight subepicardial fibrosis with minor lymphocytic infiltration; myocardium slightly degenerated; mitral valve thickened and distorted, changes being characteristic of rheumatic residuum; coronary arteries normal save for slight intimal proliferation and rhexis of elastica in one of main branches. *Lungs* present moderate emphysema accompanied by thickening of many septa as result of endothelial proliferation and leukocytic infiltration (rheumatoid interstitial pneumonitis). *Spleen* retains normal architecture, Malpighian bodies being slightly smaller than usual, many containing no so-called germinal centers; an intrafollicular hyalin material, appearing sometimes as conglomerated erythrocytes, sometimes as collagenous transformation of the reticulum, noted; there is increase in cells of the reticulo-endothelial system, the sinus endothelium being hypertrophic; occasional megakaryocytes, usually with pyknotic nuclei, lie in sinuses; moderate arteriolar thickening and hyalinization present. *Lymph nodes* exhibit reticulo-endothelial hyperplasia, architecture being preserved. *Kidneys* show no lesions other than cloudy swelling of the convoluted tubular epithelium; an entrapped megakaryocyte is noted in a glomerular tuft. *Liver* architecture normal, the epithelium being swollen and granular; occasional hypertrophic Kupffer cells are seen; portal triads appear normal. *Pancreas* the seat of slight interlobular fat infiltration but otherwise quite normal. *Appendix* moderately fibrosed but shows no definite lesion. *Adrenals* present partial loss of cortical lipoid material; eosinophilic bodies at corticomedullary junction particularly prominent. *Bone marrow:* Sternum is about 90% cellular, about half the cells belonging to the erythropoietic series, with occasional megaloblastic foci; red blood cell formation is of the normoblastic type and most of the cells are observed in this late stage of differentiation. Granulopoiesis is also of normal type with complete intramedullary maturation of neutrophils; eosinophils are somewhat more abundant than usual. Megakaryocytes are particularly prominent, usually with abundant cytoplasm and more or less pyknotic nucleus; the cytoplasm of the more degenerate forms often contains one or more neutrophils and monocytes; megakaryoblasts are encountered frequently, either as hypertrophied mononucleated cells or in a state of beginning nuclear segmentation. In 4 instances megakaryocytes situated in immediate juxtaposition to blood sinuses are observed to present the so-called "Wright's figures," i. e., cytoplasmic pseudopods extending through the sinus wall into the lumen (Plate I, A and B). Cells of the general reticulum are rather more prominent than usual and may be seen differentiating toward megakaryoblasts or myeloblasts, the latter particularly in the periphery of bone trabeculae and sinus margins.

The vertebral marrow contains slightly more fat than the sternal, being about 80% cellular, and shows somewhat less erythropoiesis than in the sternum, a rather unusual circumstance; the incidence of megakaryocytes, however, is approximately the same. Rib marrow resembles the vertebra very closely.

CASE 2.—An Italian boy (C. C.), aged 13, was admitted to the Philadelphia General Hospital (service of Dr. Warmuth; attending, Dr. Wright) on December 26, 1934 with diagnosis of acute appendicitis. His illness began December 23, 1934 with severe upper abdominal pain followed by nausea, vomiting and pain shifting to right lower quadrant. *Past History:* Patient has "bruised easily" all his life and small cuts have often bled for a week;

extensive hemorrhage followed tooth extraction at 10; after violent exercise joints would swell and become painful, the knees being most frequently involved. *Family History*: Probably first generation of hemophilia (careful inquiry into maternal family history being quite negative); patient's mother and her sister have each borne hemophiliacs, the former 3, the latter 2; bleeding time of brother  $1\frac{1}{2}$  minutes, coagulation time,  $9\frac{3}{4}$  minutes (control for method, 1 and 4 minutes respectively). *Physical Examination*: Well-developed adolescent showing normal head, neck, lungs and heart; abdomen extremely tender in right lower quadrant with suggestion of mass above anterior superior spine; peristalsis absent in this region but active elsewhere; rectal tenderness on right; both knee joints enlarged but not tender. *Laboratory Tests*: Urine shows trace of albumin, a few leukocytes and many granular casts; leukocytes 18,650 (neutrophils 88%, lymphocytes 6%, monocytes 5%, basophils 1%); platelets 260,000; coagulation time,  $11\frac{1}{2}$  to 14 minutes; bleeding time  $1\frac{1}{2}$  to 8 minutes (control as above); blood Type IV. *Course*: December 25, 1934, removal of ruptured gangrenous appendix and drainage of periappendiceal abscess; marked oozing of blood, especially from omentum; December 26, 1934, oozing continued; no response to theelin, thymus extract, thromboplastin or transfusion. December 27, 1934, bleeding continuously from drain; progynan had no effect. December 28, 1934, tympanites and vomiting; bleeding definitely lessened by thromboplastin injected into drainage tract. December 29, 1934, profuse vomiting followed by death.

*Necropsy*: (P. G. H., 28656, 5 hours after death, Dr. R. W. Mathews). Well-developed male, height 158 cm., weight 46.3 kg. with recent oblique surgical scar in right lower abdominal quadrant. Peritoneum covered by thin layer of soft, clotted blood; omentum drawn over intestines in right lower quadrant. All organs are pallid and on section ooze very little blood. *Aorta* of normal caliber and elasticity. *Heart* weighs 220 gm. (aortic valve, 5.5 cm.; mitral, 7.5 cm.; tricuspid, 10 cm.; pulmonary, 6 cm.); no anatomic lesions except for pallor of myocardium. *Lungs* are soft and crepitant, left weighing 280 gm., right 290 gm., blood-tinged frothy fluid being expressed from the cut surface. *Spleen* weighs 130 gm. and measures 12 by 7 by 3.5 cm. with thin capsule, soft, gray-red parenchyma in which follicles are visible. *Kidneys* weigh 150 gm. each, left measuring 11.5 by 4 by 3 cm.; right, 12 by 3 by 4 cm.; the thin capsules strip readily leaving smooth surfaces; cut edges slightly rounded and corticomedullary ratios normal. Lower urinary tract and genitalia are essentially normal. *Gastro-intestinal tract* is normal, except for terminal ileum and cecum which form the center of an inflammatory mass in right lower quadrant. This is well walled off from the general peritoneal cavity by the omentum and contains a small hematoma. The appendiceal and mesoappendiceal stumps are obviously the source of hemorrhage. *Liver* weighs 1340 gm. and presents a pale brown, soft parenchyma; *gall bladder*, *pancreas* and *adrenals* appear normal. *Skeleton* is apparently normal; bone marrow is pale pink.

*HISTOLOGY*. *Heart* presents marked degenerative changes in the congested myocardium. *Lungs* are congested and edematous and the seat of bacterial colonization within septa, both coccal and bacillary. *Spleen* presents small follicles without germinal centers and hyperplasia of reticular and endothelial elements, fixed and wandering, in the pulp. A single megakaryocyte is noted in a sinus. *Lymph nodes* retain normal architecture, distorted through hyperplasia of cells of reticulo-endothelial system, the sinuses being filled with macrophages. *Kidneys* are normal save for cloudy swelling of convoluted tubules and venous engorgement. *Liver* epithelium is swollen and granular; Kupffer cells are prominent and seen occasionally in various stages of detachment. Cecum presents a thickened wall extensively infiltrated by macrophages, the mucosa covered by blood and fibrinopurulent exudate. *Adrenal cortex* has lost considerable lipoid, medullary cells being



degenerated and central vein recently thrombosed. *Bone marrow*: Sternum is approximately 70% cellular, the granulocyte series being slightly in excess of the erythrocyte progenitors; maturing forms of each group are structurally normal. Megakaryocytes are noted mostly in a degenerated state as judged by marked nuclear pyknosis, karyolysis, cytoplasmic vacuolization and fraying of cell margins; cells of this series are considerably in excess of the control group (Table 2). Vertebral marrow is somewhat more cellular and shows a predominance of cells of the granulocyte series. Megakaryocytes are more numerous than in sternal marrow and normal forms are seen as frequently as degenerated cells.

**CASE 3.**—A Jewish boy (M. U.), aged 13, was admitted to the Hospital of the University of Pennsylvania (service of Dr. Gittings) December 11, 1934. His illness began suddenly the day before with sore throat, headache, fever and productive cough; "prune juice" sputum, high fever and delirium on day of admission. *Past History*: No undue hemorrhage after circumcision, first sign of hemophilia being sublingual bleeding for 4 weeks without apparent

#### PLATE I.

(All sections from Case 1.)

A. Bone marrow (sternum)—young megakaryocyte on sinus margin with two Wright's figures (WF) projecting into sinusoid; adjacent cells are erythroblasts and normoblasts ( $\times 598$ ). In the sinus, whose lumen extends beyond the margin of the figure, the lower platelet projection is the longer and paler of the two. It is limited below by a darker staining, oblong erythrocyte. B. Bone marrow (vertebra)—another megakaryocyte on sinus margin showing a short, blunt Wright's figure (WF); degenerated megakaryocyte in lower left ( $\times 598$ ). C. Bone marrow (vertebra)—showing megakaryoblast, developing megakaryocyte and degenerate megakaryocyte, adjacent cells being chiefly erythroblasts ( $\times 598$ ). D. Bone marrow (rib)—essentially the same picture as C ( $\times 598$ ). E. Heart—coronary arterial wall above presents proliferative intimal thickening; myocardial fibers show slight degenerative changes ( $\times 103$ ). F. Lung—emphysema and interstitial pneumonitis (rheumatoid) ( $\times 92$ ). G. Spleen—margin of follicle showing several thickened and hyalinized arterioles; megakaryocyte seen in lower right ( $\times 69$ ). H. Lymph node with prominence of reticular and wandering cells ( $\times 322$ ). I. Kidney—glomeruli are normal and convoluted tubular epithelium shows cloudy swelling ( $\times 92$ ). J. Liver—cloudy swelling of epithelium; normal portal triad in upper right ( $\times 103$ ). K. Pancreas—normal artery with normal island to left; parenchyma shows no lesions ( $\times 92$ ). L. Adrenal—zona fasciculata in lower half, cells being poor in lipid; zona reticularis crosses center and medulla lies above; wall of central vein in upper left ( $\times 103$ ).

#### PLATE II.

A. Bone and marrow (sternum—Case 3)—low power of cross section showing normal trabeculation and partially fatty marrow. B. Bone marrow (sternum—Case 3)—showing megakaryocyte adjacent to dense focus of erythropoiesis ( $\times 598$ ). C. Bone marrow (femur—Case 3)—showing predominance of granulopoiesis; degenerated megakaryocyte lies in midleft ( $\times 598$ ). D. Bone marrow (sternum—Case 2)—several degenerated megakaryocytes; about equal numbers of erythropoietic and granulopoietic cells compose the background ( $\times 598$ ). E. Bone marrow (vertebra—Case 2)—three megakaryocytes; other cells are predominantly erythroblasts ( $\times 598$ ).

#### KEY FOR ILLUSTRATIONS.

ERBL—erythroblast; ERC—erythrocyte; FC—fat cell; L—lymphocyte; MBL—myeloblast; MGBL—megablast; MKBL—megakaryoblast; MKC—megakaryocyte (normal); MKC-D—megakaryocyte (degenerated); MLC—myelocyte; MMLC—metamyelocyte; NBL—normoblast; PMLC—promyelocyte; R—reticulum cell; WF—Wright's figure.

Letters are placed when possible immediately below the cell indicated; a small addended "s" indicates a group of cells of the same type. All bone marrow sections stained by modification of Maximow's azure II-eosin; other viscera stained with hematoxylin-eosin; paraffin sections; photomicrographs, by Gosner and Sheppard, Phila. Gen. Hosp., with Leitz apochromatic optical system; Wratten and Wainwright M plates.

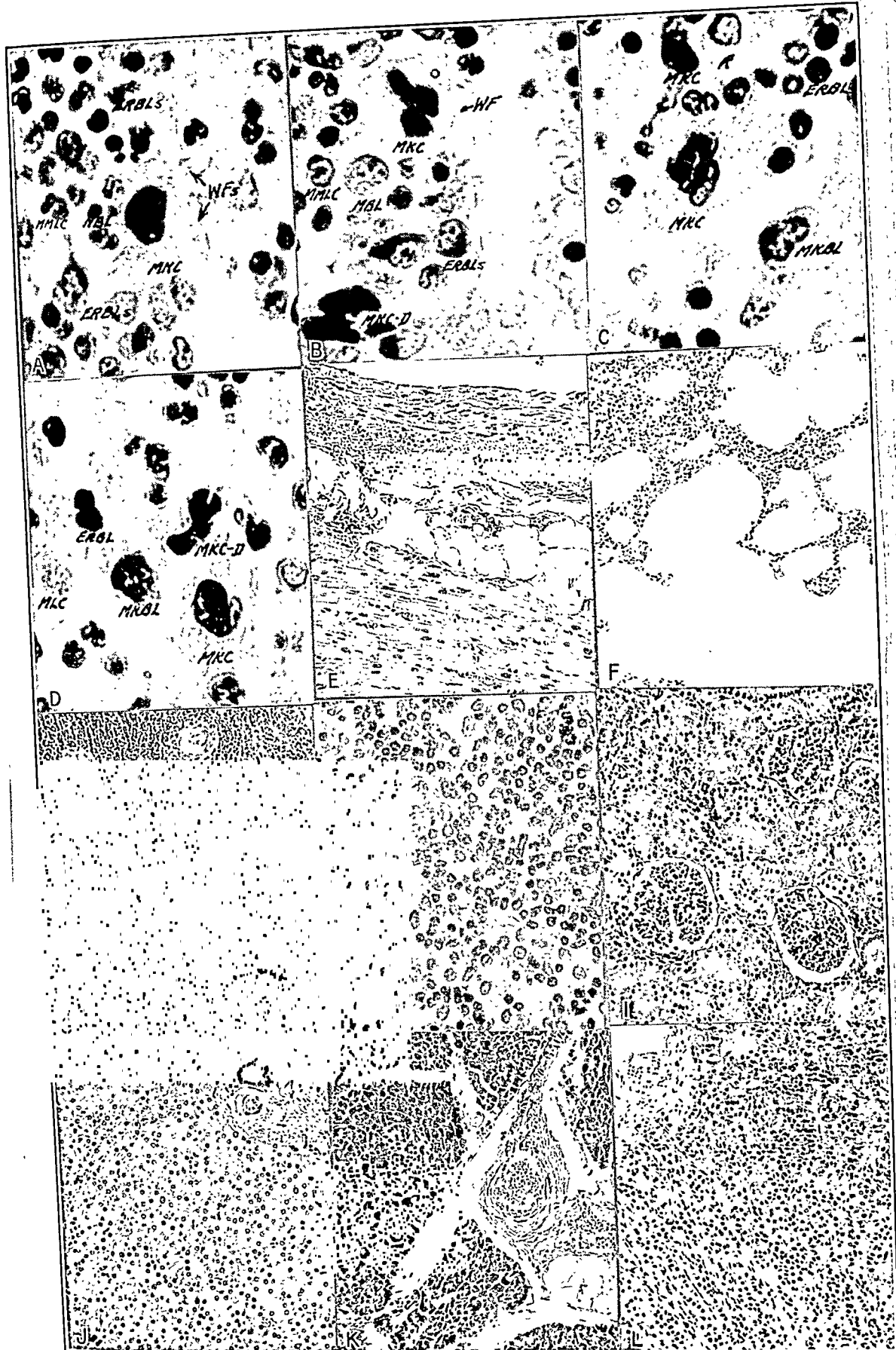
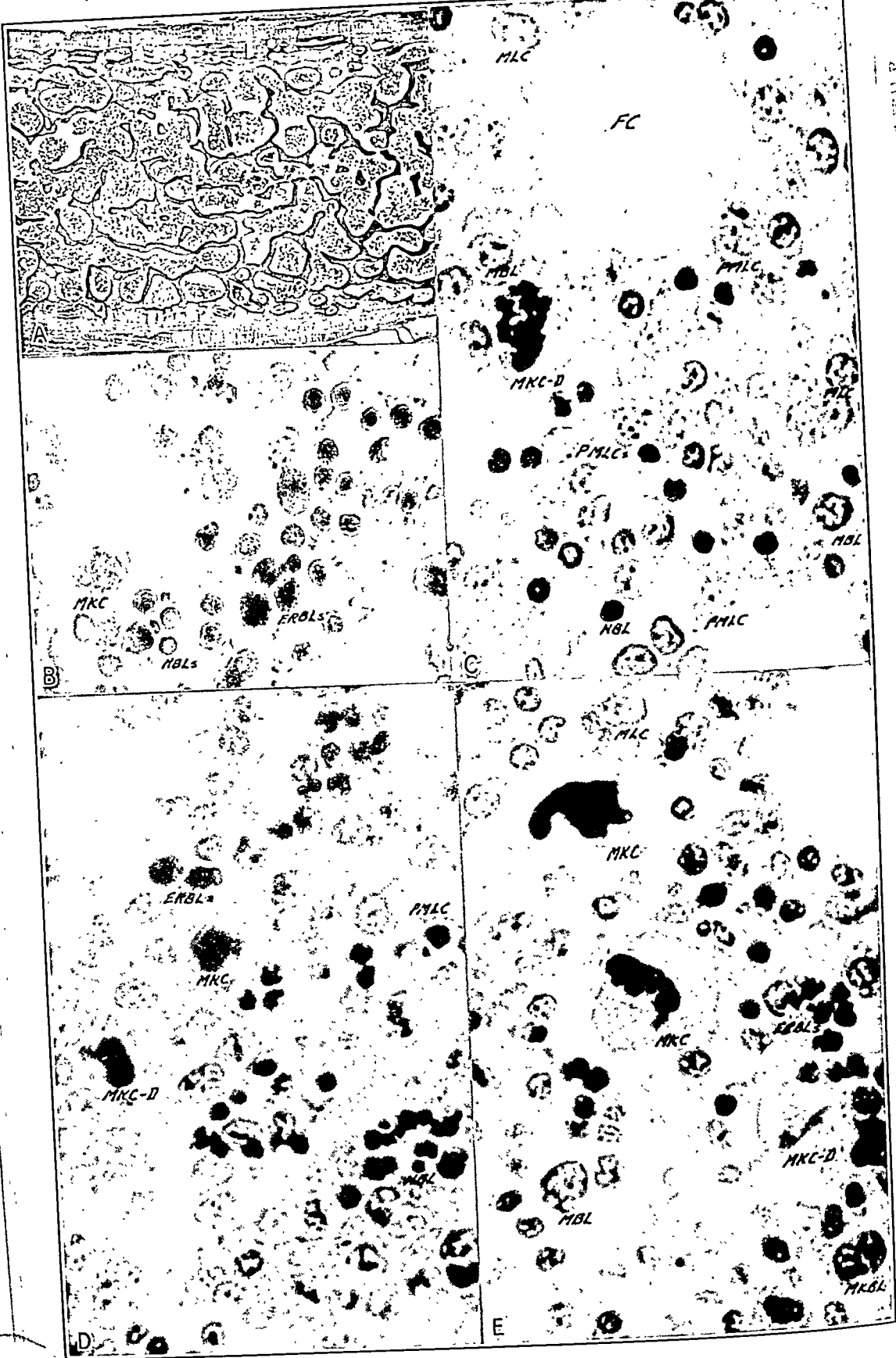


PLATE I.



# PLATE II.

FIG. 4.—Case 3. Roentgenogram, taken on November 1, 1951.

cause at 10 months; minor bruises resulted in large hematomata and several minor cuts and a tooth extraction caused oozing for 6 weeks. Subject to frequent respiratory infections. *Family History:* Maternal grandfather, who died at 79 of other causes, had a number of prolonged bleeding episodes; oldest sons of two of his daughters were also bleeders, though in each case a daughter and another son were normal in this respect; the patient, an only child of the third daughter, was definitely hemophilic. *Physical Examination:* Undernourished child, moderately cyanotic and very toxic; lungs showed signs of consolidation over right upper and both lower lobes with few râles and suppressed breath sounds; heart sounds poor; no other findings of note. *Laboratory Tests* (obtained from admission to Mt. Sinai Hospital in 1931). Urine negative; Hgb. 75 to 50%; erythrocytes 3,680,000 to 2,630,000; leukocytes 11,700 (neutrophils 78%) to 10,900 (3700 during final illness). Blood calcium 11.7 mg.%; blood phosphorus 3 mg.%; bleeding time, 5½ minutes; coagulation time, 9 minutes, 35 seconds (no normal control done); platelets 260,000; blood Type III. *Course:* Pulse gradually weaker and death occurred 2 days after first symptom.

*Necropsy:* (U. H., '34-1316, 1 hour after death, Dr. D. R. Coman). Asthenic young male, height 144 cm., weight 32 kg., presenting pallor of skin and mucosæ; each pleural sac contains 100 cc. of serosanguinous fluid. *Aorta* is smooth, white, elastic and shows no abnormality of calibre or thickness. *Heart* appears normal except for dilatation of right chambers, weight being 160 gm. and left ventricular wall 1 cm. thick. *Lungs* present large irregular red patches over lower lobes, left weighing 310 gm., right 440 gm., cut surface showing solid, airless, hemorrhagic patches throughout left lower lobe and entire right lung, intervening parenchyma being gray and moist; pus exudes from small bronchial radicles. *Spleen* weighs 90 gm. with dark red, bloody pulp dotted by gray, pinpoint follicles. *Kidneys:* each weighs 100 gm. and shows no significant changes; lower urinary tract and genitalia are apparently normal. *Gastro-intestinal tract* appears normal throughout; mesentery contains a few bean-sized, firm, gray lymph nodes. *Liver*, weighs 1020 gm., is red-brown, firm and displays normal markings, blood oozing in moderate amount from cut surface; gall bladder and bile ducts show no gross lesions. *Pancreas, adrenals, thyroid, thymus* and *pituitary* appear normal; middle and internal ears and *brain* show no lesions. *Bone marrows* of femur, sternum and vertebra are soft and red, that from the tibia soft and yellow.

*HISTOLOGY.* *Heart* shows degenerative changes of rather marked degree in the congested myocardium. *Lungs* are congested and edematous, sections of right upper and lower lobe presenting typical picture of extensive bronchopneumonia with early abscess formation and conspicuous masses of cocci; left upper lobe is the seat of early consolidation; a few naked nuclei of megakaryocytes lie in capillaries; pleura is covered in part by fibrino-purulent exudate. *Spleen* shows a comparatively cell-poor, blood-filled pulp dotted by relatively small follicles with ill-defined centers; vascular walls are slightly thickened and occasionally hyalinized. *Lymph nodes* of the mesenteric group retain essentially normal architecture, distorted through hyperplasia of reticulo-endothelial and lymphatic cell elements. *Kidneys* display glomeruli engorged with blood and tubular epithelium that is moderately degenerated. *Liver* epithelium is swollen and granular, nuclei being somewhat faded; Kupffer cells are not prominent; portal triads appear normal. *Pancreas* shows mild degenerative changes in alveolar epithelium. *Adrenal* cortical cells contain the usual amount of lipid but show loss of cell outline accompanied by occasional nuclear pyknosis. No structural abnormality is demonstrable in the *pituitary*. *Bone marrow:* The sternum contains about 25% fat, cellular marrow being loose; engorgement of blood sinuses is particularly prominent. Cells of the erythropoietic series are in the foreground, seen mostly in the late erythroblastic and nor-

myeloblastic stages (Table 1). The neutrophil group is also active, myelocytes being the predominant type. Megakaryocytes are approximately twice normal in number, the usual degenerative-regenerative balance being maintained; nuclear morphology is about as diverse as that noted in the other cases. The vertebral marrow is somewhat more cellular, but the relative proportion of cells is approximately the same, megakaryocytes being perhaps somewhat more plentiful with fewer degenerate forms. The femur is conspicuous in the activity of the neutrophil progenitors, particularly the younger forms (myeloblasts and promyelocytes), as though the previously hypoplastic marrow has undergone hyperplasia in the direction of the immediate necessity of combating infection; megakaryocytes are also seen in predominantly blastic and normal forms (Table 2); the marrow is approximately 30% cellular. The tibia presents almost complete acellularity in the midportion of the diaphysis. Bloodvessel walls are normal.

TABLE 1.—DIFFERENTIAL MARROW COUNTS (PER CENT).  
(Azure II-Eosin.) (500 cells each.)

	Case 1.	Case 2.	Case 3.		Normal control.
	Sternum.	Sternum.	Sternum.	Femur.	Sternum.
Undifferentiated cells . . . . .	3.0	0.0	0.0	3.6	0.0
Granulocyte series.*					
Myeloblasts . . . . .	3.2	5.4	2.2	12.6	0.6
Promyelocytes (neutrophil) . . . . .	5.4	9.8	8.2	20.0	9.0
(eosinophil) . . . . .	0.2	0.4	0.2	0.4	0.0
Myelocytes (neutrophil) . . . . .	7.4	22.8	13.2	9.2	34.6
(eosinophil) . . . . .	1.8	4.6	1.4	1.0	2.0
Metamyelocytes (neutrophil) . . . . .	13.8	6.0	4.8	4.6	14.6
(eosinophil) . . . . .	0.4	0.8	0.4	0.2	0.0
Segmenters (neutrophil) . . . . .	6.8	1.6	2.0	0.8	3.0
(eosinophil) . . . . .	0.0	0.4	0.0	0.0	
	— 40.6	— 51.8	— 32.4	— 48.8	— 63.8
Erythrocyte series:					
Megaloblasts . . . . .	3.8	0.2	0.4	0.8	0.0
Erythroblasts (early) . . . . .	8.2	6.4	7.0	6.8	14.8
(intermediate) . . . . .	8.6	15.2	10.8	8.0	
(late) . . . . .	8.4	11.6	14.4	9.0	
Normoblasts . . . . .	22.0	7.4	30.0	14.8	18.2
	— 51.0	— 40.8	— 62.6	— 39.4	— 33.0
Thrombocyte series:					
Megakaryoblasts . . . . .	0.2	0.4	0.4	0.2	0.2
Megakaryocytes (normal) . . . . .	0.6	0.2	0.4	1.6	
(degen.) . . . . .	0.8	1.6	0.6	0.4	0.8
	— 1.6	— 2.2	— 1.4	— 2.4	— 1.0
Reticulo-endothelial apparatus:					
Reticular cells . . . . .	3.6	2.8	1.8	3.6	2.0
Endothelial cells . . . . .	0.8	1.0	0.0	1.4	
Wandering forms . . . . .	0.4	0.6	1.2	0.4	0.2
	— 4.8	— 4.4	— 3.0	— 5.4	— 2.2
Lymphocytes . . . . .	0.6	0.8	0.6	0.4	0.0

\* Basophils not encountered; metamyelocytes include, for simplification, all cells between myelocytes and filamented nuclear forms.

*Comment.* A number of diseases other than hemophilia can produce "bleeders" and some of these have a familial incidence. However, in these 3 cases, even though hematologic studies are not all that might be desired, the diagnosis seems clear. The typical familial and individual history of bleeding episodes is reinforced by the delays in clotting time, which are all the more striking as they were done by the finger prick methods rather than with venous blood. The uncontrolled addition of tissue juice by the prick method shortens the clotting time, so that deficient blood may give a normal test.

If it is delayed by this method, however, it would be as much or more delayed with venous blood.

Among the reported necropsies on hemophiliacs may be mentioned those of Grandidier, Faucherand, Proby and Colrat, Ricker, Kissinger, Voit and Paus, Keneagy, Steward and Legg, the first and last authors furnishing a more complete group of references. While detailed descriptions are to be found of the size and location of hematomata, the pallor, perhaps degeneration of the organs and so on, little or no histology and absolutely nothing of significance about the hemopoietic organs is to be found, save for Ricker's statement that the vertebral and femoral marrows were not hyperplastic and Schmidt's reference to his postmortem examination of a case some years earlier which failed to reveal anything abnormal. His remark that nothing was yet known about the pathologic anatomy of hemophilia continued to be justified.

Though a discussion of the pathogenesis of hemophilia is beyond the scope of this paper, it may be briefly stated that for many years various factors have been held responsible for the bleeding. Virchow's authority for a long time focussed attention on Blagden's observation of unnatural thinness of vessel walls, an item that we have not observed in our 3 cases. Sahli postulated a local condition in the wall to account for the spontaneous hemorrhages, in addition to blood changes responsible for delayed coagulation of the blood, which, of course, is present even between attacks. Incriminated have been: (a) an excess of antithrombin (Weil), (b) calcium deficiency (Wright), (c) thrombokinase deficiency (Morawitz and Lossen), (d) qualitative defect in prothrombin (Nolf and Herry, Addis, Feissly and Freed, and Eagle) and (e) qualitative changes in the platelets (Fonio, Lee and Minot, Howell). The last two views have the most adherents today, the platelets on account of the morphologic changes noted and their observed delay in breaking up under experimental conditions, the prothrombin defect because a proper assemblage of components will produce normal plasma clotting with hemophilic platelets and under certain conditions hemophilic plasma still clots slowly when normal platelets are added. Quick's recent work tends to relieve prothrombin of responsibility. The matter still awaits elucidation; a possibility of both factors being contributory remains *sub judice*, especially in view of Howell's statement that platelets may contain prothrombin. Any information then, about the state of the hemopoietic tissues, especially of the megakaryocytes from which the platelets are derived, should be on record.

The state of the thrombocyte series in the bone marrow was the striking feature in all 3 cases, even though the cause of death was different in each. The extent of numerical increase in this series of cells was not fully appreciated until estimations of the incidence in approximately 12,000 cells per bone was compared with similar estimations in a group of non-hemophilic controls (Table 2). The

differences in the percentages of the thrombocyte group in Tables 1 and 3 indicate the need for an estimation covering a much larger number of cells than the usual differential count of 500 or even 1000 in categories that are sparsely represented; a method which we have found satisfactory is described briefly in the following article.

TABLE 2.—GROSS ESTIMATION OF THROMBOCYTE SERIES.\*  
(200 consecutive fields, averaging 60 cells each) (expressed as number per 12,000 total cells and in per cent of the 12,000).

	Megakaryo- blasts.		Normal megakaryocytes.		Degen. megakaryocytes.		Total.	
	No.	%.	No.	%.	No.	%.	No.	%.
Hemophilia:								
Case 1.—Sternum . . .	12	0.10	21	0.18	36	0.30	69	0.58
Vertebra . . .	16	0.13	21	0.18	35	0.29	72	0.60
Case 2.—Sternum . . .	7	0.06	6	0.05	32	0.27	45	0.38
Vertebra . . .	8	0.07	26	0.22	25	0.21	59	0.49
Case 3.—Sternum . . .	8	0.07	20	0.17	23	0.19	51	0.43
Femur . . .	16	0.13	23	0.19	9	0.08	48	0.40
						Average	57.3	0.48
Non-hemophilic controls:								
Symptomatic purpura . . .	6	0.05	10	0.08	15	0.12	31	0.26
Symptomatic purpura . . .	1	0.01	2	0.02	15	0.12	18	0.15
Polycythemia vera . . .	4	0.03	20	0.17	20	0.17	44	0.37
Chronic hemorrhage . . .	4	0.03	9	0.08	13	0.11	26	0.22
Arsphenamin neutropenia . . .	4	0.03	16	0.13	7	0.06	27	0.23
Third degree burn . . .	5	0.04	12	0.10	13	0.11	30	0.25
Brain tumor . . .	2	0.02	8	0.07	21	0.18	31	0.26
Bronchopneumonia . . .	6	0.05	11	0.09	14	0.11	31	0.26
						Average	29.7	0.25

\* For method employed see following article.

The relative percentage in the 3 hemophiliacs was fairly uniform and, surprisingly enough, in 2 cases the number in each of two different bones varied by only 3 cells. As shown by the larger cell count, the constancy of the megakaryocyte content of marrow in unselected non-hemophiliacs was remarkable, falling within a range of 5 cells except for a case of severe symptomatic purpura in profound pansinusitis which showed comparative paucity, and an increase in a case of polycythemia vera in which megakaryocytes are usually described as being plentiful. An average in hemophilia of 57.3 cells of the megakaryocyte series per 12,000 total cells opposed to 29.7 in 8 non-hemophilic controls is regarded as significant. It is worthy of note that the largest percentage of megakaryocytes appeared in the purely hemorrhagic case, the smallest in the purely infectious and a midposition held by the case in which hemorrhage was a minor factor; the increased incidence of megakaryoblasts, evidence of regenerative activity, was associated with hemorrhage, matched only by the apparently recently hyperplastic femur in the infectious case, in which the increase in young forms was offset by the sparsity of degenerate cells. Even in normal marrow a so-called degenerative-regenerative balance between normal and degenerate megakaryocytes is maintained and the close juxtaposition of a young and an effete cell occurring fairly frequently led one of us in a previous paper to suggest the possibility that the stimulus to new formation is furnished by a "nekro hormone" liberated by the degenerate cell.

The morphology of megakaryocytes in this disease does not vary from the normal. The megakaryoblast is seen as a hypertrophic,

moderately basophilic cell which may be strictly mononuclear or may exhibit early nuclear polymorphism, nuclear lobes occasionally appearing to lie one upon the other; the vague acidophilic granularity is rarely seen in this stage. The normal adult megakaryocyte presents a more or less vesicular nucleus which is multilobated with sharp perinuclear membrane, fine chromatin strands and prominent nucleoli lying in a large cytoplasmic mass with pale basophilic background and extremely delicate pink-staining granules. The degenerate cell is characterized by a shrunken or faded nucleus and a frayed vacuolated cytoplasm which stains poorly. On four occasions it was possible to demonstrate the so-called "Wright's figures," *i. e.*, cytoplasmic buds of megakaryocytes which extend through the wall of a blood sinus into the lumen, confirming J. H. Wright's observations on the mechanism of platelet formation; two such cells are pictured (Plate I, *A* and *B*).

Formation of erythrocytes and granulocytes in all 3 cases conformed strictly to normal standards. Erythropoiesis seemed rather more active in the flat bones of all 3 cases than one usually finds except in the severe anemias. The femur of Case 3 offered a contrast in that red blood cell formation was subordinate, as though hyperplasia in the long bones occurs as the needs of the situation demands, in this instance the production of neutrophils to combat infection. Eosinophilic myelocytes were unduly prominent in the marrow of Case 2, the reason not being apparent. Cells of the general reticulum appeared normal and transition toward megakaryoblasts and myeloblasts could be traced. The marrows were too complex for the demonstration of Doan's capillaries. Although the femur in Case 3 was moderately hyperplastic, the tibia was entirely fatty, supporting the view that the femur is a fairly good index of increasing bone marrow activity, and that the tibial marrow is among the last to become hyperplastic.

Details of various visceral changes are not worthy of comment except for a few points. It can be safely stated that no structural abnormality of bloodvessels can be demonstrated; the vascular thickening and distortion in Case 1 were undoubtedly rheumatic. The accessory blood-forming organs, namely spleen and lymph nodes, showed no significant changes, although an increased prominence of cells of the reticulo-endothelial system was noted in each case; there was no evidence for or against the autochthonous formation of the megakaryocytes seen in the spleen of Case 1; naked megakaryocyte nuclei were observed in the lung and kidney capillaries, indicating that they, at least, were embolic. Megakaryocytes in the blood stream and in organs other than the bone marrow have, however, been observed in various conditions.

**Summary.** 1. Three fatal cases of hemophilia with necropsy are reported, 1 dying from uncomplicated hemorrhage, 1 from appendicitis and hemorrhage, and 1 from fulminating pneumonia.



2. The hemopoietic tissues all showed normal regenerative ability, the first two predominantly erythroblastic, the third leukoblastic.

3. All three showed a marked increase of megakaryoblasts and megakaryocytes in the bone marrows, indicating a relationship of the blood platelets to the hemophilic process.

4. J. H. Wright's observation of platelet formation in the bone marrow sinusoids from intruding pseudopods of megakaryocyte cytoplasm was supported by our findings.

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#### A NOTE ON DIFFERENTIAL CELL COUNTS OF BONE MARROW. WITH SPECIAL REFERENCE TO THE ESTIMATION OF INFREQUENTLY APPEARING CELL TYPES.\*

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THE differential count of cells of the bone marrow is not a simple matter, particularly when one is dealing with sectioned material.

\* No. VI of the "Studies on the Structure and Function of Bone Marrow."

For those accustomed to the study of blood films, the marrow count is comparatively easy when obtained from well prepared smears (teased tissue suspended in serum and streaked as with blood) or imprint preparations (bits of marrow touched to the slide) stained by the method routinely used with blood. Unquestionably individual cell morphology is best brought out by this method. If one is concerned with the relative proportions of various cell series, however, the smear or imprint preparation is not accurate, in that closely packed cell clumps do not tend to disperse or may even adhere to marrow interstices and not be included on the slide. We believe that careful differential counts of marrow sections give truer information regarding the status of the hemopoietic tissue.

Of necessity, thin sections well stained by one of the Romanowsky modifications (azure II-eosin, eosin-methylene blue, eosin-orange G-toluidin blue, dilute Giemsa, etc.) must be employed. The optical system of the microscope should be such that a magnification of about 1500 diameters is attained, for example, with a 1.2 mm. oil-immersion objective and a 15 $\times$  ocular; the higher magnification is of particular importance in that there are fewer cells per field, thus admitting less possibility of confusion. An ocular micrometer is practically a necessity and may be either of the net type or the two-parallel-line variety, the latter being the one usually employed in reticulocyte estimations; the choice is a matter of personal taste.

TABLE 1.—COMPARISON OF COUNT OF FIRST AND SECOND 500 CELL GROUPS.

	Best fit.*		Poorest fit.†	
	First 500.	Second 500.	First 500.	Second 500.
Granulocyte series:				
Myeloblasts . . . . .	175	185	25	11
Promyelocytes (neutrophil) . . . . .	14	12	36	24
Myelocytes (neutrophil) . . . . .	1	1	73	115
Myelocytes (eosinophil) . . . . .	0	1	9	3
Metamyelocytes (all types) . . . . .	0	0	67	89
Segmenters (all types) . . . . .	0	0	162	100
	— 190	— 199	— 372	— 342
Erythrocyte series:				
Megaloblasts . . . . .	19	16	0	2
Erythroblasts . . . . .	92	95	32	60
Normoblasts . . . . .	102	97	43	61
	— 213	— 208	— 75	— 123
Thrombocyte series:				
Megakaryoblasts . . . . .	4	7	2	0
Megakaryocytes . . . . .	7	7	4	2
	— 11	— 14	— 6	— 2
Reticulo-endothelial apparatus:				
Reticular cells } . . . . .	50	47	18	14
Endothelial cells }				
Wandering cells . . . . .	4	9	23	15
	— 54	— 56	— 41	— 29
Lymphocyte series:				
Lymphocytes . . . . .	23	19	5	3
Plasmocytes . . . . .	9	4	1	1
	— 32	— 23	— 6	— 4

\* Case of idiopathic agranulocytosis.

† Case of septic neutropenia.

*Differential Count of All Cell Types.* Until recently we regarded a count of 1000 cells as none too extensive. Comparison, however, of the percentage obtained in the first 500 cells with that of the second showed, to our considerable relief, negligible difference for the more frequently represented cell types; Table 1 lists the best and poorest examples now on hand.

Identification and tabulation, then, of 500 cells are deemed sufficient. Dr. Neil McLeod tells us that he has had the same experience and agrees that 500 is the optimum number for the chief groups.

The procedure is best (but not necessarily) carried out by two individuals, an observer and a recorder, the former tallying total cells on a hand tabulator. The list of cell types to be identified is prepared beforehand and the recorder tabulates the cells as called. The number of cell varieties is too great to permit the use of any instrument such as the Marbel blood cell calculator. In a given delineated field all cells of a particular type may be counted and the total given to the recorder before passing on to the next cell type in the list, or cells may be tallied as they are met by proceeding systematically through the field.

An effort is necessary to eliminate as far as possible the personal factor in the count, *i. e.*, the subconscious temptation to stop at choice fields containing perhaps particular cell types in which the observer is interested. Our habit is to count every fourth field, avoiding only those containing bone trabeculae or large blood sinuses. The interpretation of cell morphology varies slightly with different individuals and the terminology employed by the three main schools of hematology is considerably at variance; comparison, therefore, is most reliable when the marrow counts have been done by the same observer.

About 5% of cells encountered cannot be identified accurately and are best completely omitted rather than listed by guess; this figure varies in direct proportion to the degree of degeneration present in the tissue. If the number is unduly large, a statement to this effect should be made in the report.

*Estimation of Infrequently Appearing Cells.* The ordinary count of 500 can hardly represent accurately the incidence of a type of cell which is sparsely and irregularly distributed in the tissue. A method of estimation involving many fields and great numbers of cells would naturally narrow the limits of error. In the previous article, for example, the cells of the megakaryocyte group were under surveillance; empirically we decided to note the incidence of these cells in 200 consecutive fields. All cells in each of 10 fields were counted in each of the 14 marrows studied by this method and an average obtained (for the optical system employed the average was 60 [59+] cells per field with a scatter from 49 to 70); this was further checked from time to time; thus the number of megakaryocytes in 200 fields (*i. e.*, approximately 12,000 cells total) was

recorded and the percentage calculated. Encroachment of fat cells, bone trabeculae and blood sinuses on the field is avoided as much as possible; when fat is plentiful, half-fields can be estimated. The constancy of these figures was remarkable, much more so than that shown in the full differential count of 500 or even 1000 cells, demonstrated clearly by comparison of Tables 1 and 2 in the preceding article.

We feel that the similarity of the megakaryocyte percentages in the control cases constitutes support for the validity of this method.\* It is obvious, however, that averages must usually be obtained for each marrow studied, and that if the cellular density of the fields varies greatly in any one marrow, the method is not suitable. The error involved in taking an average number of cells per field appears to be much smaller than that incurred by examining the smaller number of cells. Thus, if the maximum observed variation of figuring on 50 cells per field instead of 60 (or an estimation error of about 16%) was assumed in the sternal marrow of Case 3 (see preceding paper), the percent of megakaryocytes would only be changed from 0.43 to 0.51, whereas the 500 cell method gave 1.4%.

## CHRONIC GRANULOCYTOPENIA OF FIVE YEARS' DURATION WITH RECURRENT ACUTE ATTACKS.

### CASE REPORT.

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BECAUSE of the widespread interest in granulocytopenia (agranulocytic angina, malignant neutropenia, granulopenia), I am reporting a case of chronic primary granulocytopenia which has been under my observation for 5 years. The chief value of the study lies in the length of time the case has been under observation; the blood counts made daily or at regular intervals over this period of time; and the complete picture it presents of the chronic primary type of the disease—the characteristics of the acute episodes, the subjective and objective findings before, and during the intervals between, attacks, and the blood pictures during the various periods of the cycle of the disease.

**Case Report.** The patient, a woman, aged 33, had never consulted a physician prior to this illness. After the sudden death of her first husband,

\* For those who wish to get accurate percentages of sparse cell types and mistrust a method based on an average number of cells in fields that may vary considerably, it is suggested that after the 500 cell count has been finished, the count be continued without allocation of cell types other than those under special consideration, depending on the patience of the observer, until at least 5000 cells have been covered.

in 1927, she had noticed periods of extreme exhaustion in which she seemed to need more rest than usual, but she attributed this exhaustion to irregular hours of eating and resting following his death.

In November, 1929, 5 months after her second marriage, she had a very profuse menstrual period accompanied by cramping pain in the pelvis. Because of amenorrhea for the preceding 3 months and severe nausea of 1 week's duration, this was diagnosed by a gynecologist as a spontaneous abortion. Codein and morphin were given for relief of the pain and, as the uterine bleeding persisted, gynergen and ergot were administered; aspirin, allonal, amytal and sodium luminal were prescribed for restlessness and general aching. One week later she experienced chilly sensations, pain in the eyes and the feeling that her head was expanding. The next day she had a definite chill. She consulted no physician at that time but took large amounts of allonol. Three days later I saw her for the first time.

Besides the generalized aching and chilly sensations, the patient complained of pain over the precordial area, pain in and around the eyeballs and sharp, shooting pains in the long bones. The uterine hemorrhage and pelvic pain had completely subsided. Her temperature was 102° F. A diagnosis of influenza was made, but because of the possibility of an early encephalitis a neurologist was consulted and a spinal puncture was done. The spinal fluid was normal in all respects. The 5 blood counts made at this time, November 11 to 18, 1929, revealed a depression of the total leukocyte count, and upon 1 occasion an almost complete absence of neutrophils (Table 1).

During the first half of 1930 the patient had a urinary disturbance characterized by dysuria with considerable albumin and numerous pus cells in the urine. She had no other symptoms and experienced no other disturbance. During 1931 she had no symptoms of sufficient importance to cause her to consult a physician. The findings of an occasional urinalysis were normal.

On January 12, 1932, another attack similar to that of November, 1929, occurred (Table 1). She recovered from this attack but continued to complain of exhaustion, aching and occasional rises in temperature.

On April 13, 1932, the patient experienced a sudden severe chill with a temperature of 103° F. Her appearance was that of a desperately ill person. A blood count revealed the presence of only 800 leukocytes, of which but 4% were neutrophils. She was sent immediately to the hospital where nucleotide was given according to the directions of Jackson and his coworkers with results in accord with their experience. The course was a stormy one but the apparent response to the nucleotide, though gradual, was continuous (Table 1). A culture from the blood taken during this attack disclosed the presence of an organism later identified as a diphtheroid streptococcus. Shortly after the attack the organism was recovered also from the cervical canal.

The syndrome of aching, easy fatigue, precordial pain with slight irregularity of the pulse, periods of loose stools and occasional rises in temperature persisted.

A complete physical reëxamination now revealed three possible sources of infection: cervix, right tube and appendix. Because of the possibility that infection might be playing a part in her condition it was recommended that the cervix be cauterized, which was done, and that the pelvis and appendix be investigated as soon as the condition of the patient should permit such a procedure.

On November 2, 1932, another acute attack occurred. Nucleotide was given again and again apparent response was noted in increasing numbers of leukocytes and a gradual return of neutrophils (Table 1).

A month later, as the patient felt very well subjectively, an abdominal

exploration preceded by a curettage of the uterus was performed. The cervical os was somewhat stenotic as a result of previous cauterization. The abdominal organs were normal in appearance and to palpation and no gross lesions could be found. Both ovaries and both tubes were normal in appearance as was the uterus. Appendectomy was performed.

Following the surgical procedure a typical postoperative leukocytosis with the usual postoperative neutrophilia developed (Table 3). The leukocyte count then returned to normal limits but the neutrophils and lymphocytes again assumed their previous fairly equal distribution.

In February and May, 1933, she experienced sufficient increase in symptoms and change in blood count to cause us to curtail all activity and put her at bed rest, although the expected acute attacks did not develop. The last acute episode to date occurred in September, 1933, following an acute cold (Table 1). No medication other than general supportive measures was used.

**Discussion.** The symptomatology, the clinical history, the physical findings and the blood counts taken during the acute attacks (Table 1) and during the periods of remission (Table 2) present a typical picture of the chronic primary type of the disease without ulceration.

TABLE 1.—BLOOD COUNTS MADE DURING ACUTE ATTACKS.

Date.	Leukocytes.	Neutrophils, %	Lymphocytes, %
11/12/29 . . . . .	5200	40	40
11/13/29 . . . . .	5600	35	61
11/14/29 . . . . .	3400	9	86
11/15/29 . . . . .	3800	6	84
11/18/29 . . . . .	7200	27	71
<i>Supportive Treatment Only.</i>			
1/12/32 . . . . .	2000	0	97
1/13/32 . . . . .	2100	3	94
1/14/32 . . . . .	2600	16	82
1/18/32 . . . . .	7400	40	56
1/21/32 . . . . .	4800	28	67
1/25/32 . . . . .	6000	64	34
<i>Supportive Treatment Only.</i>			
4/12/32 . . . . .	800	4	96
4/13/32 12 M. . . . .	700	0	97
2 P.M. . . . .	700	0	94
4 P.M. . . . .	850	0	98
6 P.M. . . . .	800	0	93
4/14/32 8 A.M. . . . .	880	0	93
10 A.M. . . . .	840	2	95
12 M. . . . .	1300	2	90
2 P.M. . . . .	1300		
4 P.M. . . . .	1300	3	90
6 P.M. . . . .	1750	7	91
4/15/32 8 A.M. . . . .	1700	14	86
12 M. . . . .	1600	45	54
5 P.M. . . . .	1700	16	83
4/16/32 6 A.M. . . . .	2280	35	65
12 M. . . . .	1700	33	66
5 P.M. . . . .		32	68
4/17/32 8 A.M. . . . .	2850	38	62
12 M. . . . .	2400	33	67
5 P.M. . . . .	2430	21	72

TABLE 1.—BLOOD COUNTS MADE DURING ACUTE ATTACKS.—(Continued.)

Date.	Leukocytes.	Neutrophils, %	Lymphocytes, %
4/18/32 8 A.M. . . . .	2480	30	66
12 M. . . . .	2850	27	65
5 P.M. . . . .	2620	21	78
4/19/32 8 A.M. . . . .	2700	31	
5 P.M. . . . .	3206	35	61
4/20/32 A.M. . . . .	3730	34	66
P.M. . . . .	4410	31	77
4/21/32 A.M. . . . .	3950	44	56
P.M. . . . .	4550	31	68
4/22/32 A.M. . . . .	4500	45	53
P.M. . . . .	4100	23	74
4/23/32 A.M. . . . .	4100	42	58
P.M. . . . .	4500	45	52
4/24/32 A.M. . . . .	5250	48	48
P.M. . . . .	5400	50	46
4/26/32 . . . . .	7400	45	50
	9100	49	45

*Nucleotide Therapy.*

10/31/32 . . . . .	6500	52	44
11/ 2/32 A.M. . . . .	3400	73	27
P.M. . . . .	3000	79	21
11/ 3/32 A.M. . . . .	1700	26	68
P.M. . . . .	1200	12	84
11/ 4/32 A.M. . . . .	1500	2	89
M. . . . .	1400	0	93
P.M. . . . .	1100	0	100
11/ 5/32 A.M. . . . .	1300	1	95
P.M. . . . .	1200	5	88
11/ 6/32 A.M. . . . .	2600	21	72
P.M. . . . .	2200	24	71
11/ 7/32 A.M. . . . .	3200	52	46
P.M. . . . .	3200	46	52
11/ 8/32 A.M. . . . .	3200	45	53
P.M. . . . .	3500	44	54
11/ 9/32 A.M. . . . .	3600	42	57
P.M. . . . .	4600	39	59
11/10/32 . . . . .	4700	49	47
11/11/32 . . . . .	6400	59	37

*Nucleotide Therapy.*

9/11/33* 9 A.M. . . . .	2400	6	48
11 A.M. . . . .	2600	6	53
1 P.M. . . . .	4050	2	70
3 P.M. . . . .	4150	4	62
5 P.M. . . . .	5000	8	64
7 P.M. . . . .	5250	7	60
1/12/33 9 A.M. . . . .	6100	14	57
11 A.M. . . . .	6000	12	61
1 P.M. . . . .	4950	8	76
5 P.M. . . . .	5650	14	57
9/13/33 9 A.M. . . . .	4950	13	73
11 A.M. . . . .	5800	17	58
9/14/33 . . . . .	8500	17	58
9/18/33 . . . . .	10,300	57	42

*Supportive Measures Only.*

\* I am indebted to Dr. S. R. Mettier of the University of California Hospital in San Francisco for the blood counts and data obtained during this attack which occurred while the patient was visiting in that city.

TABLE 2.—BLOOD PICTURES DURING PERIODS OF REMISSION.  
(Averages of Counts Made.)

Date.	Leukocytes.	Neutrophils, %	Lymphocytes, %
2/ 9/32 to 3/24/32 (14 counts) . .	6521	48	48
4/28/32 to 10/ 5/32 (25 counts) . .	8128	57	39
11/12/32 to 12/ 3/32 (daily counts) .	5643	38	56
12/14/32 to 1/31/33 (daily counts) .	7756	43	53
2/11/33 to 4/24/33 (daily counts) .	7494	46	48
5/10/33 to 9/ 7/33 (45 counts) . .	7064	44	52
9/19/33 to 1/16/34 (23 counts) . .	9321	54	41
2/ 1/34 to 6/ 1/34 (38 counts) . .	6154	55	40
6/ 1/34 to 12/31/34 (28 counts) . .	6135	59	35

TABLE 3.—NORMAL POSTOPERATIVE LEUKOCYTOSIS.

Date.	Leukocytes.	Neutrophils, %	Lymphocytes, %
12/ 4/32* . . . . .	8,800	37	54
12/ 5/32 . . . . .	10,100	47	41
12/ 6/32 . . . . .	11,400	63	32
12/ 7/32 . . . . .	12,000	78	16
12/ 8/32 . . . . .	9,500	72	26
12/ 9/32 . . . . .	8,500	66	27
12/10/32 . . . . .	8,200	55	39
12/11/32 . . . . .	9,000	57	36
12/12/32 . . . . .	8,000	43	54
12/13/32 . . . . .	6,775	52	43
12/14/32 . . . . .	8,800	40	57

\* Date of operation.

TABLE 4.—INCREASE IN NEUTROPHILS FOLLOWED BY REVERSAL OF NEUTROPHIL-LYMPHOCYTE RATIO—A POSSIBLE INDICATION OF ONCOMING ACUTE ATTACK.

Date.	Leukocytes.	Neutrophils.	Lymphocytes.
10/31/32 . . . . .	6500	52	44
11/ 2/32 . . . . .	3400	73	27
P.M. . . . .	3000	79	21
11/ 3/32 . . . . .	1700	26	68
P.M. . . . .	1200	12	84
11/ 4/32 . . . . .	1500	2	89
2/ 3/33 . . . . .	7100	47	50
2/ 4/33 . . . . .	7500	63	33
2/ 5/33 . . . . .	5600	74	25
2/ 6/33 . . . . .	4000	32	63
2/ 7/33 . . . . .	6200	19	71
2/ 8/33 . . . . .	5800	28	66
2/ 9/33 . . . . .	6400	47	50
2/10/33 . . . . .	8900	45	50
4/29/33 . . . . .	7500	53	43
5/ 1/33 . . . . .	4900	61	37
P.M. . . . .	2600	37	58
5/ 2/33 . . . . .	2400	16	79
P.M. . . . .	4300	10	82
5/ 3/33 . . . . .	5000	19	79
5/ 4/33 . . . . .	7200	39	59
5/ 5/33 . . . . .	6400	37	59
5/ 6/33 . . . . .	7800	52	40
5/ 8/33 . . . . .	7700	49	48



The blood pictures reveal one finding of particular interest. On 3 occasions (November 2, 1932, February 5, 1932, May 1, 1932) an increase in neutrophils was noted a few hours before, after or at the same time that the total leukocyte count started to fall (Table 4). The fall of the neutrophil count from this higher point was abrupt and caused a complete reversal of the neutrophil-lymphocyte ratio. It is possible that such an increase in neutrophils may be used as an indicator of an oncoming acute attack.

Because of a possible relationship between certain drugs and granulocytopenia, in April, 1933, the patient was asked to discontinue all drugs of the benzin ring. At this time she told me that she had done this voluntarily after the first acute attack in 1929, as she thought that the allonol which she had taken in large amounts at that time might have been responsible for the blood picture.

Nucleotide was given in 2 of the most severe attacks. The rise in the leukocyte and neutrophil count corresponded to the results apparently obtained by its use by Jackson. Supportive measures only were used during the other less severe attacks.

During the periods of remission various forms of medication have been tried. An autogenous vaccine from the diphtheroid streptococcus found in the blood stream and cervical canal resulted in no apparent improvement. Antuitrin intramuscularly and thyroid extract orally were given over a period of several months because of irregularity of menstruation and the fact that her first definite attack occurred with a delayed menstrual period and presumed abortion, and because a possible connection between this disease and glandular imbalance has been suggested by some authors. This form of therapy produced no apparent change in symptomatology or blood picture. Bone marrow was given and was discontinued after a month's trial, during which no improvement was noted, because of untoward symptoms of nausea, vomiting and dysentery.

Concentrated forms of vitamins B and D, in addition to a well-balanced diet, have been given empirically since June, 1934. During this time there has been apparent improvement in subjective symptoms and a rise in the general level of the leukocytes and the neutrophil-leukocytes to within normal limits. We are continuing this line of treatment on the basis that granulocytopenia may be a deficiency disease in the same way that pernicious anemia is a deficiency disease. However, until the question of the etiology of the disease is determined by further observations and experimental work, our treatment can be only empirical and its value determined by results obtained.

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CYTOPLASMIC CHANGES IN THE PERIPHERAL NEUTROPHIL  
AS AN AID IN DIAGNOSIS AND PROGNOSIS.

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OUR purpose is to call attention to a hematologic finding which we feel to be of proven clinical importance as an aid in diagnosis and prognosis and as a guide to the course of infectious disease. Except for a few American investigators (Kugel and Rosenthal,<sup>1</sup> Rosenwasser and Rosenthal,<sup>2</sup> Rosenthal and Sutro,<sup>3</sup> and Sutro<sup>4</sup>), this matter has been neglected in our country, though utilized to advantage by continental, particularly German, workers. Recent textbooks of hematology in our language fail to treat the subject adequately. Adler,<sup>5</sup> commenting upon the vast amount of clinical information to be gained by this examination of the blood, deplored the fact that alterations in the cytoplasm of neutrophils had been studied less than those of the nuclei.

Cytoplasmic changes in the peripheral neutrophil, as we have studied them, consist briefly of an alteration of the staining quality of the cytoplasm and its components from a normal eosinophilic pink to a dirty gray or blue. There is also usually an increase in granulation. In the normal neutrophil the cytoplasmic granules are fine, regularly dispersed and oxidase positive. In the abnormal cell they are coarse, irregular in distribution, staining a deep blue and oxidase negative. They may be sparse, grouped on one side, or diffusely scattered over the entire protoplasm. All the neutrophils are not uniformly granulated. In some the granules may be so large that the cell may be mistaken for a basophil. In addition, vacuolization of the cytoplasm is usually observed, giving the cells a moth-eaten appearance about the periphery or throughout the cytoplasm. These three changes, alteration of the staining character of the cytoplasm, abnormal granulation and vacuolization, have been regarded by most authors on the subject as toxic or degenerative changes, indicative of severe disease process, and when pronounced and progressive, to denote an unfavorable prognosis.

As early as 1908, Cesaris-Demel<sup>6</sup> spoke of these changes as degenerative, the vacuoles being due to loss of fat content of the

protoplasm; the poor staining quality he noted in cells "about to die" and termed it a process of autophagocytosis. He also observed the excessive granulation and regarded the prognosis as always improved when it disappeared from the cells. Türk<sup>7</sup> offered a complete description of toxic changes in granular leukocytes in various diseases in 1912. Mommsen,<sup>8</sup> with a special Giemsa stain diluted with a buffered solution of pH 5.4, showed that normal granules stained weakly compared to these abnormal granules. He termed the latter "pathologic or toxic" and stated that pathologic granulation is a measure of the intensity of the infection afflicting the patient. Barta<sup>9</sup> showed that one could differentiate by a study of these changes between localized and generalized infection and that increasing toxic cytoplasmic changes indicated increasing gravity of outlook. It is interesting to note that, in 1923, just 2 years before Minot and Murphy's discovery of liver treatment for pernicious anemia, at a time when such theories as infection by various organisms, particularly *B. welchii* and *B. coli*, were considered in discussions of the etiologic nature of this disease, Naegeli,<sup>10</sup> impressed with the persistent absence of pathologic alterations of the cytoplasm of the neutrophils in pernicious anemia and their frequent presence in infectious processes stated: "This finding alone is sufficient to convince me that the cause of pernicious anemia is not infectious." He<sup>11</sup> is so convinced of the regularity of this finding in severe infections that he uses its absence to militate against the belief of the infectious origin of acute leukemia. He further feels that the regularity with which these granulations occur in the neutrophils seen in agranulocytosis point to an infectious origin of this disease.

Spaeth<sup>12</sup> demonstrated with Mommsen's technique that in various infectious diseases the occurrence of pathologic cytoplasmic changes depended on the intensity of the infecting agent; the more virulent the latter the greater the toxic alterations of the cells. He also showed that the Schilling-Arneth shift did not always parallel these toxic changes. Matis,<sup>13</sup> corroborating this, maintained that when the toxic granulation is marked one must think not only of an infection but must consider a very grave prognosis. Adler<sup>5</sup> believes the granulation is due to absorption of toxin or to destruction of protein material, and in the graver septic conditions he finds vacuolated cytoplasm. Gloor<sup>14</sup> has done extensive work upon the subject. He has described two types of granules in infections; in mild cases the small granule now known as the "A granule of Gloor," and in severe cases the coarse, heavy granule known as the "B granule of Gloor." The bodies described as the Döhle bodies in scarlet fever, Gloor attributes to a toxically induced alteration in the staining quality of the neutrophil cytoplasm.

As to the nature of these changes, Naegeli<sup>10</sup> has pointed out that they do not occur in the bone marrow but only in the cells of the

circulating blood. A toxic effect upon the bone marrow usually produces alterations in the nuclei of the neutrophils. He finds cytoplasmic changes occurring in diseases particularly affecting mesenchymal tissues and states that the leukocytic cytoplasmic changes parallel the mesenchymal damage. Gloor demonstrated that the degree of absorption of pathologic substance from inflammatory foci had more to do with the pathologic cytoplasmic changes than the apparent local severity of the disease process. The greatest degenerative changes, for instance, were found near the crisis in pneumonia, when the greatest absorption of toxic products occurs. He further found that the more extensive the absorbing surface in a disease process the greater the toxic changes in the neutrophilic cells; hence in localized infections as appendicitis there would occur fewer cytoplasmic changes; whereas in peritonitis, with a large absorptive surface, marked toxic changes occur. In empyema, as the disease process becomes older and more encapsulated, the pathologic blood cytoplasmic changes become less pronounced, presumably because the pleural surface becomes less absorptive.

Schilling<sup>15</sup> attributes these cytoplasmic changes to degenerative phenomena, while Naegeli feels they are due to toxic effect associated with suppuration. Barta suggests that they represent phagocytosed particles. Their exact nature is still debatable. Quite recently, however, Hirschfeld and Moldowsky<sup>16</sup> report having found pathologic granular changes in the neutrophils of normal healthy Roentgen ray workers; hence they conclude the phenomenon is by no means a pathologic one, but rather a reactive change occurring in infection and under such influences as the Roentgen ray.

**Present Study.** Our study consists of a group of 250 cases of infectious and non-infectious diseases from the wards of Mount Sinai Hospital on which 1500 examinations were made, employing the Jenner-Giemsa staining method. We used Rosenthal's degenerative index, an excellent simple method for quantitatively measuring this phenomenon. The index is the percentage obtained by dividing the number of abnormal neutrophils by the total number of neutrophils studied in the smear. In general, our findings coincide with those of other authors, except those of Hirschfeld and Moldowsky. We have been unable to demonstrate these abnormal cytoplasmic states in Roentgen ray workers or in patients receiving Roentgen ray treatment. However, we have examined only a limited number and intend later to investigate the subject more thoroughly. At present we wish to report the findings in the diseases studied and indicate the value from a diagnostic and prognostic viewpoint derived from this study.

**Pneumonia.** This disease, above all others, is most uniformly characterized by cytoplasmic neutrophilic changes with high degenerative indices. Indeed, the frequency with which this phenomenon is present in lobar and severe lobular pneumonia should make one

hesitant in diagnosing these conditions in the absence of toxic granulation. The persistence of a high percentage of cells showing toxic cytoplasmic changes for some time after the crisis should warn the attending physician of a grave complication. During the crisis these changes frequently increase, but they slowly decrease and finally disappear with convalescence. We have studied 43 such cases: 25 of lobar pneumonia, 10 of lobular pneumonia, 2 diagnosed clinically pleural pneumonia, 1 diagnosed metastatic pneumonia, 1 diagnosed pneumonitis and 4 cases of empyema.

*Lobar Pneumonia.* Of the 25 cases, 20 yielded degenerative indices of 50% or more, with 5 less than 50%—1 with 0%. However, this latter patient was diagnosed lobar pneumonia by an unsatisfactory bedside Roentgen ray, the clinical course not bearing out the diagnosis. Nevertheless, including all cases, the average degenerative index found by us in lobar pneumonia was 60%. In many cases the degenerative index was more informative of the patient's condition than the total leukocyte count.

*Pneumonia Series.*

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
L. S.*	77	16.0-19.0	98-100
F. C.*	45	4.4-11.5	34- 83
M. N.*	2	47.0-29.0	87- 61
A. S.*	27	9.0-27.9	90- 76
Y. G.*	60	17.8	63
H. O.*	45	18.0	83
S. M.*	76	29.7	17
J. R.	50	19.2- 8.2	68- 20
M. S.	23	23.8-12.9	51- 5
W. H.	2	20.4-19.3	90- 20
E. M.	3	17.3-13.2	15- 0
S. H.	8	17.0-10.2	50- 31
S. L.	20	32.1-14.2	13- 0
A. L.	5	26.7- 7.9	70- 62
E. B.	20	11.4- 7.2	90- 0
S. F.	1	25.6-12.2	76- 25
R. N.	7	29.5-15.5	52- 0
J. G.	6	25.8-16.5	31- 14
S. B.	14	31.4- 8.9	55- 0
D. G.	4	23.7-14.6	92- 74
F. A.	19	20.4	84
E. W.	22	17.0	58
I. S.	2	17.5-15.2	61- 50
J. F.	50	11.1- 7.1	0
D. H.	3	22.3- 9.0	83- 46

\* Died.

*Illustrative Cases.* CASE 1.—F. C., male, aged 45, was admitted to service of Dr. A. I. Rubenstone, on February 23, 1934, having been ill for 2 days prior to admission with fever, dyspnea, cyanosis and stitch-like pain in left lower chest. Temperature, 101.6° F.; pulse, 120; respirations, 36 per minute. Clinical diagnosis: Lobar pneumonia involving left lower lobe. C. B. C.: 93% hemoglobin, 4,770,000 erythrocytes, 4400 leukocytes, with 42 non-segmented and 52 segmented neutrophils and 6 lymphocytes. Degenerative index, 34%. Roentgen ray examination confirmed clinical

diagnosis. Artificial pneumothorax therapy was used; 500 cc. of air was injected into the left pleural space and repeated within 12 hours. Next day the general condition was poorer, temperature and toxicity persisted, the total leukocyte count was 7900 with 55 non-segmented and 40 segmented neutrophils. Degenerative index, 45%; on the following day, February 25, he was worse; the total leukocytes were 11,500 with 59 non-segmented and 38 segmented neutrophils; the degenerative index had risen to 83%. He expired on this day.

CASE 2.—E. B., male, aged 20, was admitted to the service of Dr. A. I. Rubenstone, on February 27, 1934, for chill, pain in chest aggravated by deep breathing, cough and blood-tinged sputum. Temperature, 104° F.; pulse, 100 to 120; respirations, 28 per minute. Clinical diagnosis: Lobar pneumonia of left lower lobe, confirmed later by bedside Roëntgen ray examination. Blood chemistry and serology normal; blood culture sterile. Sputum: Type I pneumococcus. Blood count: 87% hemoglobin, 4,300,000 erythrocytes, 11,400 leukocytes with 1 myelocyte, 32 non-segmented and 55 segmented neutrophils, 7 lymphocytes and 5 monocytes. Degenerative index, 40%. The following day the total leukocyte count rose to 18,300, differential similar to original examination, and degenerative index 55%. He was given 80,000 units of antipneumococcic serum (Type I) within 24 hours in addition to usual supportive measures. The next day, March 1, total leukocyte count was 17,900, differential same and degenerative index now 90%. Clinical condition remained unchanged. On March 2, temperature fell sharply to normal by crisis and remained there. On March 6, after steady improvement, total leukocyte count was 12,800 with 17 non-segmented and 62 segmented neutrophils. Degenerative index had dropped to 48%. On March 12, a slight leukocytosis persisted but the degenerative index reached 0%. On March 15, patient was discharged as cured—leukocyte count now normal and degenerative index 0%.

*Lobular Pneumonia.* In these 10 cases the degenerative index followed the clinical picture as accurately as did the temperature and more accurately than did the total leukocyte count. Four cases had degenerative indices of 50% or more, 5 cases had less than 50% and 1 case showed no toxic cytoplasmic changes. The average degenerative index was 45%, or 15% less than in lobar pneumonia. Cases of lobular pneumonia in children demonstrated the highest toxicity in the neutrophils in this series.

*Lobular Pneumonia Cases.*

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
I. K.*	3	16.0-6.2	5-91
J. M.*	2	33.4	62
S. S.	1	37.0-17.2	72-27
M. G.	1	21.2	62
L. B.	1	12.7	35
M. L.	34	8.5-18.0	45-0
M. J.	7	15.4-10.5	16-0
W. B.	21	9.5	0
B. L.	65	7.8-5.6	30-0
J. S.	56	10.5-6.8	9-20

\* Died.

*Pleural Pneumonia.* This is a term used by some clinicians to designate a form of pneumonitis characterized by fever, mild

toxicity, diminished breath sounds, questionable impairment and râles of pleuritic rather than parenchymal origin, *i. e.*, in which a diagnosis of consolidation cannot be made. These patients are usually not as ill as the cases classified lobar or lobular pneumonia and the diagnosis of pneumonia in them is always doubtful. Occasionally a mild pneumonia may be present in this group; more often the case is one of uncomplicated pleurisy. We had 2 such cases. Both showed no toxic cellular alterations, and the probability is that they were not pneumonic. There was also 1 case diagnosed "pneumonitis" with a degenerative index of 60%. It is more than likely that this patient had pneumonia with indefinite physical signs, since on the seventh day of her disease a sustained temperature of 103° F. dropped by crisis to normal and remained so.

#### *Pleural Pneumonia Cases.*

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
R. P. . . . .	30	17.0	0
J. S. . . . .	8	25.8	0
E. C. . . . .	13	8.1	60
M. C. . . . .	53	13.2-9.1	26

Diagnosed "pneumonitis."  
Pneumonia complicating pulmonary infarction.

*Empyema.* All cases showed toxic cytoplasmic changes in proportion to the degree of illness. One died with a mounting degenerative index which reached 62%; the other 3 cases recovered and their degenerative indices gradually dropped to zero with recovery.

#### *Empyema Cases.*

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
J. M.* . . . . .	2	33.4	62
J. G. . . . .	7	35.7-14.0	45-8
J. G. . . . .	2	21.8	20
J. Z. . . . .	4	32.7-14.9	50-11

\* Died.

*Fatal Cases in Pneumonia Group.* There were 9 fatal cases: 7 of lobar and 2 of lobular pneumonia. In 8 of these the degenerative index ranged from 65% to 100%, averaging 82%. In the other, a proven case of lobar pneumonia in an aged male, the degenerative index was 17%. However, this patient lived in the hospital but 12 hours, only one examination was made and the smear was reported before examination as poorly stained.

*Otitic Infections.* Forty-seven cases of ear diseases were studied. Five cases of otitis media (Group A) and 17 cases of uncomplicated mastoiditis (Group B) showed no toxic cytoplasmic changes in the neutrophils, which finding paralleled mild clinical courses and uneventful convalescences. None of these 22 patients manifested any marked evidences of toxemia, sepsis or complications. Un-

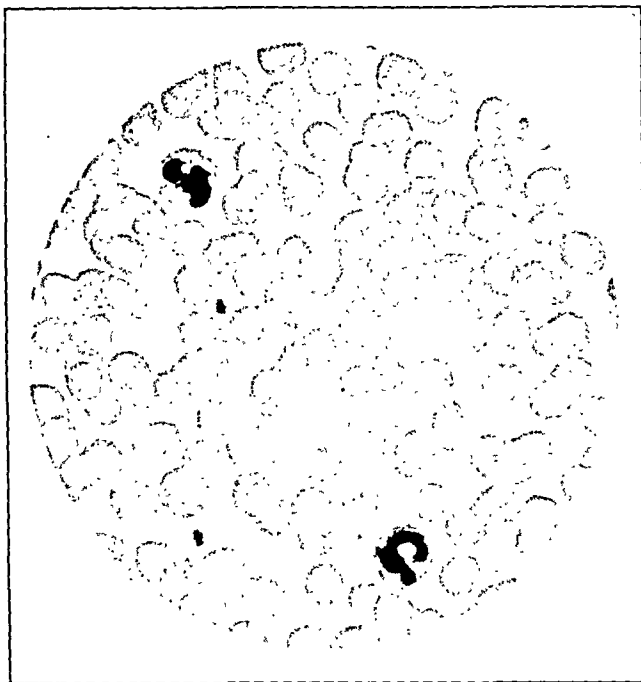


FIG. 1.—Blood smear showing cells without toxic granulations. Normal blood.  
( $\times 700$ .)

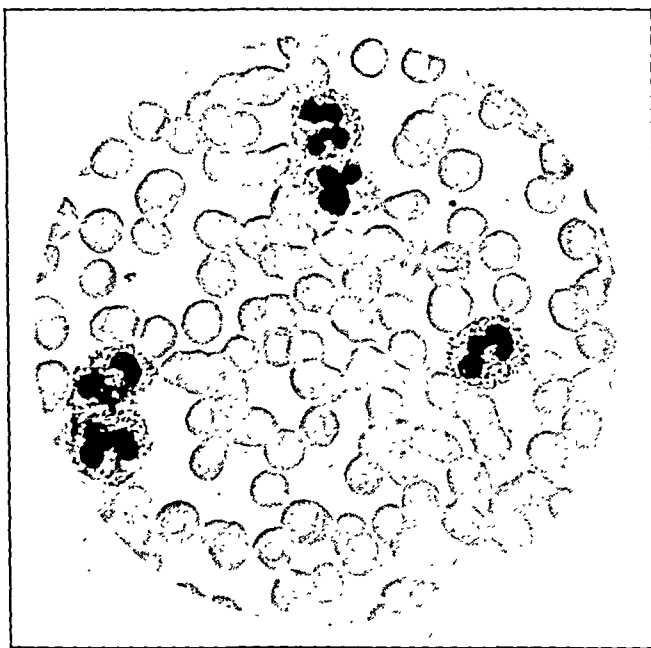


FIG. 2.—Blood smear showing cells with toxic granulations. From a case of lobar pneumonia. ( $\times 700$ .)





eventful recoveries were never in doubt. The total leukocyte counts ranged from 15,000 to 28,000.

Group A		Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
Patient.	Age.		
M. D. . . . .	4	19.9	0
E. G. . . . .	3	15.4-13.7	0
S. P. . . . .	18	16.3	0
S. P. . . . .	2	21.8	0
I. Z. . . . .	1	15.6- 6.1	0
Group B			
J. C. . . . .	10	18.2	0
P. S. . . . .	3	28.7	0
L. I. . . . .	6	16.5	0
S. I. . . . .	17	17.3	0
L. S. . . . .	7	23.8	0
P. S. . . . .	5	23.2-13.0	0
S. A. . . . .	1	15.2- 9.3	0
M. T. . . . .	46	10.9- 8.6	0
M. N. . . . .	2	19.4-16.4	0
M. A. . . . .	7	19.8	0
J. H. . . . .	6	20.9	0
L. W. . . . .	1	19.3	0
H. S. . . . .	7	25.7	0
B. S. . . . .	6	18.8	0
B. L. . . . .	4	15.6	0
M. B. . . . .	9	16.4	0
H. N. . . . .	11	12.8	0

In Group A the average stay in the hospital was 6 days. In Group B the diagnosis was confirmed by Roentgen ray examination and operation in 14 cases and by Roentgen ray examination in the remaining 3. The average period of hospitalization in this group was 11 days.

The remaining 25 cases evidenced toxic cytoplasmic changes varying from slight to a very intense nature. All had septic, stormy stays in the hospital and their degrees of illnesses were at all times comparable to the height of their degenerative indices. In some cases in which toxic changes occurred it was the first phenomenon to warn of the developing gravity of the condition. Of these 25 patients, 13 (Group C) developed diagnosable complications, namely, pneumonia, meningitis, erysipelas, adenitis, lateral sinus thrombosis, etc. As already shown by Group B, uncomplicated localized mastoiditis will not produce toxic cytoplasmic neutrophil changes; hence it can be stated that the toxic changes in this group were due entirely to the complications. As might have been anticipated, pneumonia produced the highest degenerative indices. Meningitis, it has been shown by others, does not produce these changes unless accompanied by bacteriemia. This observation was in accord with our findings in 2 cases, 1 with a complicating streptococcic meningitis yielding no toxic changes and the other with an otitic meningitis and a 25% degenerative index which could be ascribed to other factors. One case in this group, complicated

by erysipelas, demonstrated no toxic changes which we were unable to explain. The average period of hospitalization in this group was 48 days, which when compared to the 11-day period in Group B gives some idea of their illnesses.

Group C		Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; complications.
Patient.	Age.		
M. K.*	6	30.8	25 Otitic meningitis.
I. K.*	3	16.0-6.2	5-91 Bronchopneumonia.
J. M.*	4	12.8-17.8	0 Streptococcic meningitis.
D. H.	3	22.3-9.0	83-46 Lobar pneumonia.
W. H.	3	20.4-19.0	96-20 Lobar pneumonia.
F. B.	2	24.8-13.2	75-20 Erysipelas and adenitis.
C. G.	6	18.2-14.2	0 Erysipelas.
C. G.	7	23.3-13.9	28-11 Erysipelas and adenitis.
M. D.	7	13.8-11.4	0-35 Erysipelas.
D. G.	4	10.7-6.6	23-24 Lateral sinus thrombosis.
I. S.	2	15.2-17.5	61-50 Lobar pneumonia.
E. W.	9	20.4-20.2	50-28 Lateral sinus thrombosis.
E. H.	36	9.1	41 Suppurative pansinusitis.

\* Died.

Twelve cases of mastoiditis (Group D) showed toxic cytoplasmic changes. Whether these are the result of undiagnosed complications or very severe grades of mastoiditis we are unable to say. All had very septic courses with high degrees of morbidity; they were all quite as sick after mastoidectomy as before, and all gave their attending physicians grave concern. Their average length of morbidity was 19 days as compared to 11 days of Group B.

Group D		Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
Patient.	Age.		
O. R.	4	28.2-15.5	42-18
J. L.	3	24.9-12.8	58-5
R. W.	4	17.2-7.2	26-6
S. D.	3	15.9-10.6	45-28
M. B.	5	16.3-12.0	56-0
E. H.	6	36.0-19.6	41-12
Y. R.	12	14.3	35
W. N.	5	24.2	31
J. G.	2	23.3-17.7	28-14
B. J.	3	22.7-20.3	92-65
S. P.	7	15.6-20.5	10-16
H. N.	2	40.5-23.3	13-0

From these findings it should be expected that in dealing with uncomplicated otitis media or mastoiditis toxic cytoplasmic changes in the neutrophils should not be present. The addition of this finding to the hemogram should bring to mind the possibility of a complication or the spreading of what was until then a localized infection.

*Illustrative Case.* CASE 3.—T. C., male, aged 17 months, was admitted to the service of Dr. M. A. Weinstein, on January 31, 1934, for fever and discharge of pus from left ear. Temperature, 103° F.; pulse, 120; respirations, 40 per minute. Clinical diagnosis: acute otitis media. Roentgen

ray examination revealed chronic left mastoiditis. Blood count: Hemoglobin, 60%; erythrocytes, 3,400,000; leukocytes, 21,400; with 18 non-segmented and 58 segmented neutrophils, 18 lymphocytes and 6 monocytes. Degenerative index, 67%. The child was treated conservatively; the temperature reached 105° F. twice during the next week but only for a few hours each time. Clinically, improvement ensued and the discharge ceased. However, 2 additional leukocyte counts during this time were 21,450 and 15,200, respectively; the former showed an increase in the older neutrophils with a decrease in the younger forms, the latter with normal differential. But the degenerative indices for these counts were 81% and 70%. Nevertheless, because of clinical improvement, normal temperature, cessation of ear discharge and lowering of the total leukocyte count; in spite of the rising degenerative index the patient was discharged as improved. Within a few days he was readmitted (February 18) with a chill and temperature of 105° F. Total leukocyte count was 17,400 with 5 non-segmented and 63 segmented neutrophils, 25 lymphocytes and 7 monocytes. Degenerative index, 50%. Left mastoidectomy was performed; hemolytic streptococci recovered from mastoid cells. For a week following operation high temperature persisted; during the second week it ranged between 99° and 100° F. The total leukocyte counts dropped to normal but the degenerative indices were slower to reach zero. Patient was discharged on March 14 improved.

**Upper Respiratory Infections.** This term includes cases of acute "colds," coryza, tonsillitis, sinusitis, mild influenza and grippe. We found no toxic cytoplasmic changes in this group. When they occur in any of these conditions one should be ready to change or add to the diagnosis.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Range of degenerative index.
E. C. . . . .	5	16.3	0
F. G. . . . .	19	14.5	0
A. W. . . . .	22	11.9	0
I. N. . . . .	9	12.4	0

**Tuberculosis.** Many authors report the finding of mild toxic cytoplasmic changes in tuberculosis. However, early in the disease they are not present. They are more likely to occur in advanced cases in which the disease is making progress and in which secondary infection is a factor. Our cases were all early ones.

Patient.	Age.	Total leukocyte count, thousand per c.mm.	Percentage range of degenerative index.
L. S. . . . .	55	11.4	0
J. R. . . . .	41	9.3	0
M. C. . . . .	31	16.1	0
M. G. . . . .	57	12.7	7
M. M. . . . .	20	15.1	0

Multiple skin infection.

**Appendicitis and Peritonitis.** Eleven cases of appendicitis were studied; 6 were acute suppurative in type; all were localized to the appendix. All began with an acute attack, mild fever and leukocytosis; all were promptly operated upon, and all had normal, rapid, uncomplicated recoveries. None of these showed toxic cyto-

plasmic changes. The other 5 were complicated, 3 with localized peritonitis and the formation of pelvic abscesses demonstrating degenerative indices ranging from 25% to 50%. The other 2 were instances of perforated appendicitis with generalized peritonitis. In them the degenerative indices ranged from 50% to 74% at the height of their diseases, and with recovery the cytoplasmic degenerative changes slowly disappeared.

Two additional cases of peritonitis of considerable interest present themselves. Both had fatal outcomes, the degenerative indices attesting to the gravity of the cases. In both this examination would have thrown light upon the diagnosis. One (S. G.) was under observation for possible meningitis, though peritonitis was considered. In meningitis these cytoplasmic changes do not occur to such a degree, hence the finding of so high a degenerative index (93%) would have favored a diagnosis of peritonitis. The other case (S. T.) was an obese middle-aged female, admitted for signs of intestinal obstruction thought to be due to the presence of a large pelvic tumor. The high degenerative index (91%) should have directed attention to peritonitis as the more likely abdominal condition.

Patient.	Age.	Total leukocyte count, thousands per c.mm.		Percentage range of degenerative index; diagnosis.
L. M. . . . .	18	14.2	0	Acute suppurative appendicitis.
F. K. . . . .	24	21.4	0	Acute suppurative appendicitis.
M. M. . . . .	31	15.8	0	Acute suppurative appendicitis.
B. C. . . . .	11	22.4	0	Acute suppurative appendicitis.
L. C. . . . .	17	15.2	0	Acute suppurative appendicitis.
M. M. . . . .	20	25.4	0	Acute suppurative appendicitis.
D. M. . . . .	17	15.2	20	Acute suppurative appendicitis, with localized peritonitis and pelvic abscess.
H. S. . . . .	22	16.0	33-15	Acute suppurative appendicitis, with localized peritonitis and pelvic abscess.
M. K. . . . .	9	20.1	50-20	Acute suppurative appendicitis, with localized peritonitis and pelvic abscess.
A. W. . . . .	14	15.2	74- 0	Perforative appendicitis with generalized peritonitis.
S. A. . . . .	25	25.9	50- 0	Perforative appendicitis with generalized peritonitis.
S. G. . . . .	1	19.9	93	Primary streptococcic peritonitis.
S. T. . . . .	51	14.9	91	Generalized peritonitis secondary to gangrene of bowel due to embolism of mesenteric artery.

*Illustrative Case.* CASE 4.—A. W., male, aged 14, was admitted to the service of Dr. B. Lipschutz, on February 15, 1934, for pain in right lower abdominal quadrant of 2 days' duration accompanied with nausea and vomiting. Temperature, 105° F.; pulse, 160; respirations, 34 per minute. Clinical diagnosis: acute perforated appendicitis with peritonitis. Blood count: Hemoglobin, 82%; erythrocytes, 4,200,000; leukocytes, 15,200; with 34 non-segmented and 58 segmented neutrophils, 8 lymphocytes. Degenerative index, 6%. Ruptured appendix was removed and peritoneal

cavity drained on day of admission. In spite of general supportive measures, including blood transfusions for sepsis, the temperature remained elevated and vomiting persisted. Total leukocyte count was now 21,700 with 15 non-segmented and 75 segmented neutrophils, and the degenerative index had risen to 74%. Additional drainage was instituted on February 22 without improvement. For the next 2 days condition was grave, the total leukocyte counts and differentials remaining the same with slight variation and the degenerative index persisted at 70%. Cecostomy was done on February 24 for obstruction, and drainage now became profuse. On March 5, there was the first evidence by temperature chart that the patient was improving; the total leukocyte count was 16,400 with 40 non-segmented and 46 segmented neutrophils and a drop in degenerative index to 40%. On March 13, improvement continuing, degenerative index was 26%. On March 17, total leukocyte count was 14,200, differential nearly normal and degenerative index 4%. On March 29, total leukocytes, 6050; degenerative index, 0%. He was discharged on April 1 as cured.

**Biliary Tract Disease.** Localized infections of the liver or bile ducts yield, as a rule, no toxic cytoplasmic changes, as can be illustrated by these 7 cases. With an added complicating factor the degenerative index will rise.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
H. R.* . . . .	33	28.4-19.2	70-53 Subhepatic abscess with peritonitis following cholecystectomy.
L. S.* . . . .	65	23.4	0 Choledocholithiasis with cholemia and liver atrophy.
B. S. . . . .	78	11.8	5-29 Acute cholecystitis.
S. G. . . . .	6	15.5	0 Acute hepatitis.
E. K. . . . .	3	13.7	0 Acute hepatitis.
A. R. . . . .	70	16.9	0 Choledocholithiasis.
R. S. . . . .	33	20.8	0 Subacute cholecystitis.

\* Died.

**Miscellaneous Suppurations.** In this group of 21 cases of suppurations in various parts of the body the same rule holds true, namely, that in a localized infection in which but little absorptive surface is exposed to the infecting agent we find no cytoplasmic pathologic changes. However, in spreading infections toxic changes begin to appear in proportion to the severity and extent of the disease. Retropharyngeal abscesses yield high degenerative indices. Subpectoral abscesses with their large absorptive areas showed high degrees of pathologic cytoplasmic changes. Uncomplicated salpingitis produced no toxic neutrophilic changes, but when complicated by suppurations in the uterus, septicemia or pelvic abscesses with peritonitis, then toxic cytoplasmic changes begin to mount in degree corresponding to the extent of the surface attacked. In the 2 cases of perinephric abscesses, 1 was well localized and unassociated with toxic changes. The other was more extensive with greater invasion of perinephric spaces, and here we found 10% of the neutrophils toxic. Had operation not been performed at this

point there is no doubt that the degenerative index would have risen. Carbuncles show high toxic changes in contrast to suppurative adenitis which rarely yield such findings. Cellulitis, when slight, yields only mild toxic changes but, when spreading and associated with suppuration, the degenerative index may reach 100% and the outcome become increasingly grave. Pyelitis, with no further kidney damage and if draining, yields no toxic cytoplasmic changes.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
P. N.	7	24.5	56 Retropharyngeal abscess.
G. G.	4	21.5	42 Retropharyngeal abscess.
L. L.	5	21.4	63 Retropharyngeal abscess.
H. R.	30	14.2	70 Spreading subpectoral abscess.
P. S.	18	20.0	46 Spreading subpectoral abscess.
R. L.	29	22.6	0 Bilateral salpingitis.
R. M.	26	24.8	0 Bilateral salpingitis.
M. B.	35	10.5	28 Suppurative metritis.
I. G.	21	19.2	64 Septic abortion with septicemia.
H. M.	31	21.0	38 Suppurative metritis.
M. G.	26	18.8	66 Bilateral tuboövarian abscesses with pelvic peritonitis.
N. P.	54	16.5	0 Perinephric abscess.
H. L.	23	14.7	10 Perinephric abscess.
M. C.	42	16.2	5 Cellulitis of hand, localized.
S. L.	38	24.8	89 Spreading cellulitis with suppuration.
M. G.	42	17.2	32 Spreading carbuncle of neck.
M. L.	22	17.8	18 Inguinal abscess.
E. G.	18	20.6	0 Axillary abscess.
E. S.	9	22.4	0 Axillary abscess.
E. O.	32	30.4	0 Perirectal abscess.
B. G.	5	20.4	0 Pyelitis.

These examinations represent the height of the disease.

**Osteomyelitis.** This group of cases illustrates how an increasing degenerative index can warn the clinician of the seriousness of the outcome or predict a favorable prognosis when its steady decrease accompanies the clinical course. S. L. on admission showed no toxic cytoplasmic changes. Soon these developed and increased rapidly with each examination of the blood, finally reaching 100%, and the patient expired. C. S. on admission had a degenerative index of 83%, which after the institution of treatment gradually dropped from day to day until cure was established and the index reached zero. The other cases illustrate that acute fulminating osteomyelitis show high degrees of toxic cytoplasmic changes, whereas the chronic type demonstrates much different findings.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
S. L.*	10	14.6-12.6	0-100 With septicemia.
R. P.*	11	13.2	47 With septicemia.
I. L.	58	19.2	67
C. S.	60	25.4-10.4	83- 0
V. H.	7	8.9	22
D. R.	13	8.4	0

\* Died.

*Illustrative Cases.* CASE 5.—S. L., female child, aged 10, was admitted to the service of Dr. M. B. Cooperman, on March 2, 1934. Following mild sore throat of 2 days' duration she developed fever with pain and tenderness in the region of the right tibial tubercle. Temperature was 105° F.; pulse, 130; respirations, 26 per minute. Clinical diagnosis: acute osteomyelitis of hematogenous origin. Blood count: Hemoglobin, 76%; erythrocytes, 3,560,000; leukocytes, 14,600; with 4 non-segmented and 78 segmented neutrophils, 8 lymphocytes and 10 monocytes. Degenerative index, 0%. Blood chemistry and serology normal; blood culture sterile in 48 hours. Roentgen ray examination negative for acute osteomyelitis. Right tibia was drilled, pus located and drained. Blood transfusion and supportive measures were instituted. On March 6, child was septic and the temperature had assumed pump-handle type. Total leukocytes were 12,900, with 47 non-segmented and 30 segmented neutrophils. Degenerative index, 40%. Right knee was aspirated, considerable pus removed; organism, *Staphylococcus aureus hemolyticus*. Repeated blood culture now returned positive for the same organism as found in knee. Patient steadily went downhill in spite of all measures of treatment. By serial counts it was interesting to note how accurately the progress was followed by the mounting degenerative index. On March 7, total leukocytes, 11,000; 40 non-segmented and 32 segmented neutrophils; degenerative index, 58%. On March 9, total leukocytes, 21,000, with 22 non-segmented and 50 segmented neutrophils; degenerative index, 72%. March 12, total leukocytes, 33,400; 31 non-segmented and 52 segmented neutrophils; degenerative index, 80%. March 14, total leukocytes, 18,800; 35 non-segmented and 38 segmented neutrophils; degenerative index, 96%. March 16, the day on which the patient expired, the total leukocytes were 12,600, with 28 non-segmented and 58 segmented neutrophils, and the degenerative index 100%.

*In Contrast.* CASE 6.—C. S., male, aged 60, was admitted to the service of Dr. B. Lipschutz, on January 30, 1934, for pain and swelling of the right thigh with fever. Temperature, 103.8° F.; pulse, 130; respirations, 22 per minute. Blood chemistry and serology normal. Repeated blood cultures sterile. Blood count: Hemoglobin, 62%; erythrocytes, 3,200,000; leukocytes, 25,400, with 26 non-segmented and 68 segmented neutrophils, 5 lymphocytes, 1 monocyte. Degenerative index, 83%. Roentgen ray examination: acute periostitis. Incision and drainage of the right femur, pus found, and drained. Culture from femur: non-hemolytic streptococci. Blood transfusions and general measures to combat sepsis instituted. February 7, condition still septic; total leukocytes, 14,000, with 18 non-segmented and 74 segmented neutrophils. Degenerative index, 74%. On February 11, the temperature showed some evidence of striking a lower level and clinical improvement was apparent. Total leukocytes, 13,200, with 24 non-segmented and 64 segmented neutrophils; degenerative index, 45%. On February 19, the temperature was normal, general condition good, total leukocytes, 10,400, with 17 non-segmented and 65 segmented neutrophils; degenerative index, 26%. On February 23, the total leukocytes were 10,400, with 14 non-segmented and 54 segmented neutrophils; degenerative index, 0%. He was discharged on February 25 as cured.

**Meningitis.** There are 6 cases in this series, 5 were fatal, 1 recovered. As pointed out by Naegeli, marked toxic cytoplasmic changes in this disease are usually absent unless bacteriemia be present. In 1 case (B. C.) accompanied by a positive blood culture the degenerative index reached 76%. The others manifested slight or no toxic changes.



Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
B. C.*	2	17.5	76 Meningococcic meningitis with meningococemia.
R. S.*	4	11.8	10 Otitic meningitis.
J. R.*	23	13.8	10 Pneumococcic meningitis.
J. M.*	4	17.8	0 Streptococcic meningitis.
M. K.*	6	30.8	25 Otitic meningitis.
T. P.	1	16.8-9.8	20 Meningococcic meningitis.

\* Died.

**Erysipelas.** Most investigators have found toxic cytoplasmic changes in erysipelas. Two of our cases with adenitis showed these changes and 2 did not.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
P. D.	2	14.0	0
C. G.	6	18.2	0
C. G.	4	23.3-13.9	26-11 With adenitis.
F. B.	2	24.8-13.8	75-20 With adenitis.

**Ulcerative Colitis.** This disease usually presents mild toxic cytoplasmic changes in the neutrophils throughout its course. With increasing gravity of the case, and as the patient becomes more septic, the cellular cytoplasmic changes are intensified until a degenerative index of 100% may be reached in the advanced cachectic state. The patient who died (B. G.) demonstrated a gradually increasing degenerative index over a period of months until it reached 91% before death.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
B. G.*	16	10.0-21.4	0-91
B. B.	26	15.3	18

\* Died.

**Body Burns.** Burns, as a rule, produce no cytoplasmic neutrophil changes. However, when infection with large area for absorption is present these changes occur. In our fatal case (L. B.), the patient was hospitalized for more than 400 days, in the last few months the degenerative index steadily mounting and remaining at 100% for a few weeks before death.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
L. B.*	7	21.0-15.0	75-100 Secondary infection.
M. P.	9	20.0-18.0	0-35 Secondary infection.
M. R.	10	15.0	0 Localized, uninfected.

\* Died.

**Neoplastic Diseases.** Of these 11 cases of tumors, 6 presented no toxic cytoplasmic changes. These included 4 cases of carcinoma with and without metastasis, 1 case of Hodgkin's disease and 1 case

of non-malignant ovarian cyst. Hence, benign tumors, malignant tumors, metastasis or even fatality in this group are not causes for these changes. Five cases did demonstrate toxic cytoplasmic alterations, the degenerative indices ranging from 30% to 87%. Each of these 5 was complicated by infection, and it is highly probable that the toxic cytoplasmic changes in the neutrophils was due to the infection rather than to the neoplasm. In each case the degree of the changes paralleled the intensity of the infection. As mentioned before, 3 cases were fatal, but the degenerative index could not be used as a measure of prognosis in these cases. Barta has found toxic changes in cases of uncomplicated malignancy. We have not been able to confirm his finding.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
M. K.* . . . .	66	69.0-59.7	72-87	Carcinoma of stomach with metastasis; huge rectal and pararectal abscess.
P. B.* . . . .	56	18.6-18.0	0	Carcinoma of stomach and pancreas.
S. S.* . . . .	49	5.0	44	Carcinoma of colon; wound infection and necrosis.
S. T. . . . .	54	14.2	0	Carcinoma of stomach with metastasis.
R. K. . . . .	28	6.5	0	Carcinoma of bronchus.
H. S. . . . .	45	17.3	30	Carcinoma of breast; massive wound infection with necrosis.
A. S. . . . .	48	13.9	50	Spongioblastoma of brain; suppurative pansinusitis.
S. T. . . . .	67	12.5	0	Carcinoma of stomach.
J. M. . . . .	56	18.6-7.8	35-0	Abdominal carcinomatosis.
R. Z. . . . .	40	17.2	0	Non-malignant ovarian cyst.
F. C. . . . .	58	16.5	0	Hodgkin's disease.

\* Died.

**Cardiovascular Disease.** This series was taken as a control group. Most of these cases had non-infectious degenerative lesions of the cardiovascular system. They are compared with our groups of infectious diseases. Most of them were very ill; many were in critical condition. The acute rheumatic types were clinically active. Yet none manifested any toxic cytoplasmic neutrophil alterations. One case of coronary thrombosis yielded a degenerative index of 30%, but it was found to be due to an apical pneumonia complicating the picture. Hence, we can definitely state, no matter how ill the cardiac patient, one should not expect to find toxic changes unless secondary infection is superimposed.

Patient	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
A. A.* . . . .	50	13.2	0	Hypertensive C. V. disease with decompensation.
H. F.* . . . .	65	12.8	0	Hypertensive C. V. disease with decompensation.

Patient	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
B. L.*	50	17.5	0 Luetic C. V. disease with decompensation.
R. W.*	70	28.4	0 Arteriosclerotic C. V. disease with decompensation.
H. L.	59	19.3	0 Luetic C. V. disease with hypertension.
E. W.*	60	12.8	0 Hypertensive C. V. disease with decompensation.
E. C.	73	20.7	0 Arteriosclerotic C. V. disease with cerebral thrombosis.
R. M.	68	16.5	0 Arteriosclerotic C. V. disease.
B. P.	24	13.2	0 Rheumatic endocarditis.
D. M.	60	14.9	30 Coronary thrombosis; apical pneumonia.
S. B.	59	13.9	0 Coronary thrombosis.
J. B.	47	19.2	0 Hypertensive C. V. disease.
J. G.	19	17.6	0 Rheumatic endocarditis.
R. R.	37	15.4	0 Rheumatic pancarditis.
J. Z.	32	17.7	0 Rheumatic pancarditis with polyarthritis.
G. K.	7	16.2	0 Recurrent rheumatic endocarditis.

\* Died.

**Pregnancy.** Fifteen cases of pregnancy were studied. Many observers have reported toxic cytoplasmic changes in ruptured ectopic gestation and account for it by absorption. Whatever the explanation, our 2 cases also demonstrated this finding. Of the 7 with normal pregnancies, deliveries and puerpera, none showed any degenerative cytoplasmic alterations. The other 6 cases showed toxic cytoplasmic changes in the neutrophils, of which 5 could be attributed to septic complications in the puerperium. One case with a degenerative index of 31% manifested no complication and we were unable to explain it.

Therefore, we would conclude that in normal pregnancy without morbidity no toxic alterations in the neutrophils should occur. Their presence means definite complication by infection.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
M. M.	25	27.0-10.2	76-9 Ruptured ectopic gestation.
E. McG.	27	19.9-9.3	31-0 Ruptured ectopic gestation.
P. R.	32	7.8	0 Normal pregnancy.
G. Z.	19	13.3	0 Normal pregnancy.
S. S.	21	10.9	0 Normal pregnancy.
F. D.	26	10.6	0 Normal pregnancy.
A. S.	22	16.2	0 Normal pregnancy.
F. B.	28	26.0	0 Normal pregnancy.
A. S.	33	17.4	0 Normal pregnancy.
R. S.	25	29.5-14.9	59-11 Puerperal infection.
M. M.	27	25.8-14.7	23-59 Puerperal infection.
L. S.	28	19.4-12.2	25-75 Puerperal infection.
R. Z.	31	22.0-11.2	40-65 Puerperal infection.
M. P.	24	20.0-12.4	31-38 Puerperal infection.
D. F.	24	19.3-12.7	6-31 Normal pregnancy.

**Arthritis.** Search for toxic cytoplasmic changes in the neutrophils in various forms of arthritis proved vain. Regardless of the intensity of the illness these changes are absent. The only instance in which they may be found is when a positive blood culture is present in the infectious, rheumatic or gonorrheal types.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
D. S. . . . .	49	25.0	0 Polyarthritis.
R. W. . . . .	23	23.3	0 Gonorrheal arthritis.
R. McK. . . . .	5	17.9	0 Suppurative arthritis.
S. S. . . . .	39	16.9	0 Infectious arthritis.
J. Z. . . . .	32	17.7	0 Rheumatic arthritis.

**Renal Disease.** Toxic cytoplasmic changes are not found in the neutrophils in nephritis either of the degenerative or inflammatory types—even fatal cases present no such findings.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
F. R.* . . . .	54	8.6	0 Chronic diffuse glomerular nephritis with hypertension.
F. F. . . . .	26	8.8	0 Acute diffuse glomerular nephritis.
J. J. . . . .	5	13.7	0 Focal hemorrhagic nephritis.
I. P. . . . .	4	13.9	0 Focal hemorrhagic nephritis.

\* Died.

**Miscellaneous.** This series represents a miscellaneous group of cases non-infectious in origin all of which presented no toxic cytoplasmic changes in the peripheral neutrophils unless complicated by infection. It is of value as an additional control for comparative purposes.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
D. P.* . . . .	3	14.3	0 Hydrocephalus.
M. K. . . . .	40	17.5	0 Bronchial asthma.
L. S. . . . .	57	16.6	0 Bleeding peptic ulcer.
M. S. . . . .	24	20.2	0 Strangulated hernia.
H. R. . . . .	65	12.8	0 Hemorrhoids.
A. V. . . . .	60	15.9	0 Hypertrophied prostate.
M. R. . . . .	51	19.4	0 Fissure in ano.
W. P. . . . .	16	12.4	0 Fracture.
O. R. . . . .	28	12.0	0 Pilonidal cyst.
R. F. . . . .	31	6.2	0 Typhoid fever.
M. G. . . . .	62	19.4	0 Diabetes with gangrene.
E. S. . . . .	65	18.3-15.7	42 Hypertrophied prostate; abscess of leg.
H. S. . . . .	54	19.2	0 Acute leukemia.

\* Died.

**Summary.** The subject of toxic cytoplasmic alterations in peripheral neutrophils is presented with a discussion of the conditions in which these changes occur and those in which they are not found.

These findings have been shown to be of value diagnostically. They are most uniformly found in infections, and probably their greatest value lies in differentiating localized from generalized infections or the development of complications, whether this be a secondary infection or a spread of the initial infection. These changes are most uniformly found in pneumonia, peritonitis, bacteriemias and septicemias. The addition of toxic cytoplasmic changes in the neutrophils to the hemogram in which they were previously absent should warn the attending physician of an added complication.

From a prognostic viewpoint, an increasing degenerative index lends increasing gravity to the outcome.

The addition of this examination as a routine to the hemogram is of clinical value, often gives more information than the total leukocyte count and if followed serially is often more informative than the Arneth-Schilling shift.

No hemogram in infection or in serious disease states is complete without the determination of toxic cytoplasmic changes and their recording in some quantitative scheme, such as Rosenthal's "degenerative index."

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## MECHANISMS OF CARDIAC RHYTHM.

ILLUSTRATED BY UNUSUAL HUMAN ELECTROCARDIOGRAMS.

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THE purpose of this paper is to present unusual electrocardiograms, which elucidate the generally accepted principles of cardiac rhythm. Lewis<sup>1</sup> has stated as a law "that if several heart centers are simultaneously active, the heart as a whole will be dominated by the center which develops its rhythmic impulse most rapidly." This is true if the reservation is made that conduction both forward and retrograde is unimpaired.

In the normal mechanism, the heart is controlled by the sino-auricular node because its rate of impulse formation exceeds that of the lower rhythm centers, namely, the auriculoventricular node and idioventricular centers. When the conducting mechanism is such that conduction forward (auricle to ventricle) and retrograde (ventricle to auricle) is unimpaired, sino-auricular control can be replaced by artificial stimuli, provided the rate of these stimuli exceeds that of the sinus node.<sup>2</sup> The excitation wave will spread from the site of stimulation through auricles and ventricles, and the entire heart will respond to the new center. When the auricle is stimulated the normal sequence of contraction continues. When the ventricle is stimulated, the sequence is reversed; the ventricle contracts before the auricle and the impulse is conducted backward.

The mechanism of cardiac rhythm is modified by variations in the state of conduction between auricle and ventricle. Four possible states may be considered; (1) The conducting tissue may transmit impulses in either direction (forward and retrograde conduction equal); (2) the conducting tissue may convey impulses from auricle to ventricle only (unidirectional block<sup>3</sup>); (3) only retrograde impulses are transmitted; (4) both forward and retrograde conduction may be impaired or blocked (complete heart block).

The rhythms and spread of excitation when forward and retrograde conduction are equal has already been considered. In the second condition, unidirectional (retrograde) block, impulses originating in the auricle will reach the ventricle; but none beginning in the ventricle will be conducted to the auricle. The normal sequence of the cardiac cycle continue provided the auricular center is the most rapid. Should the rate of a ventricular center exceed that of the auricle, however, the two chambers will beat independently. The rapid ventricular stimuli control the ventricle because they submerge the slower impulses conducted from the auricle. Impaired retrograde conduction blocks the rapid impulses from the

ventricle and the auricle responds independently to the rhythm of its own slower pacemaker. The ventricular rate in such a case exceeds the auricular.

The third possibility, forward block<sup>3</sup> alone is a rare condition. It is the reverse of the preceding mechanism. Here rhythm control of the entire heart is possible when the most rapid center is in the ventricle and dissociation exists when the auricular center exceeds the ventricular center.

In the fourth condition, we have the common clinical entity of complete heart block. The rhythm and rate of each chamber may be slow or rapid. The auricular rhythm may vary as widely as that of a sinus bradycardia to that of auricular fibrillation. The ventricular rate may vary from the usual slow rate of the idioventricular center to that of paroxysmal ventricular tachycardia or ventricular fibrillation. Usually the auricles beat more rapidly than the ventricles; but in rare instances this relationship may be reversed.

The above principles of the cardiac mechanisms limit the number of possible rhythms as follows:

- I. UNIDIRECTIONAL BLOCK (RETROGRADE): This is probably the normal state of conducting tissue.
  - A. *Most rapid center in auricle.*
    1. Normal sinus rhythm.
    2. A-V nodal rhythm.
 

(a) Escaped beat	} When sinus node is depressed.
(b) Escaped rhythm	
(c) Premature beat	} When A-V nodal center is stimulated.
(d) Nodal tachycardia	
    3. Ectopic auricular rhythm.
      - (a) Premature auricular contraction.
      - (b) Auricular ectopic tachycardia.
    4. Auricular flutter.
    5. Auricular fibrillation.
  - B. *Most rapid center in ventricle*—Ventricle alone responds; auricle responds to its own center.
    1. Isolated escaped ventricular beat
    2. Escaped ventricular rhythm
    3. Premature ventricular contraction
    4. Ventricular tachycardia
    5. Ventricular fibrillation
    6. Parasystole.

1. Isolated escaped ventricular beat	} When sinus node is depressed.
2. Escaped ventricular rhythm	
3. Premature ventricular contraction	} When ectopic center is stimulated.
4. Ventricular tachycardia	
5. Ventricular fibrillation	
- II. BIDIRECTIONAL CONDUCTION—FORWARD and RETROGRADE: (Rare).
  - A. *Most rapid center in auricle*—The rhythms are the same as IA.
  - B. *Most rapid center in ventricle*—Entire heart responds and sequence of contraction is reversed. The rhythms are same as IB. Parasystoles of auricular origin cannot occur.
- III. COMPLETE HEART BLOCK—Both chambers are always independent.
  - A. Auricular rhythms—as under IA.
  - B. Ventricular rhythms.
    1. Idioventricular rhythm (origin above bifurcation of bundle tissue).
    2. Ectopic ventricular rhythm (origin below bifurcation of bundle tissue).
    3. Ventricular tachycardia.
    4. Ventricular fibrillation.

## IV. UNIDIRECTIONAL BLOCK—FORWARD—(Very rare).

- A. *Most rapid center in auricle*—Auricle alone responds; ventricle responds to its own center—Rhythms are the same as IA.
- B. *Most rapid center in ventricle*—Both chambers respond—Sequence of contraction reversed—Rhythms are the same as IIIB.

In the extensive literature on arrhythmias, the material appears in the main as individual case reports illustrating one or other of these mechanisms. Lewis<sup>8</sup> includes examples of the great majority of the possible mechanisms, some of which were obtained experimentally on animals. He does not treat them collectively but discusses each as it serves to illustrate one or other phase of the subject. It seemed useful therefore to review the subject of arrhythmias using clinical electrocardiograms only.

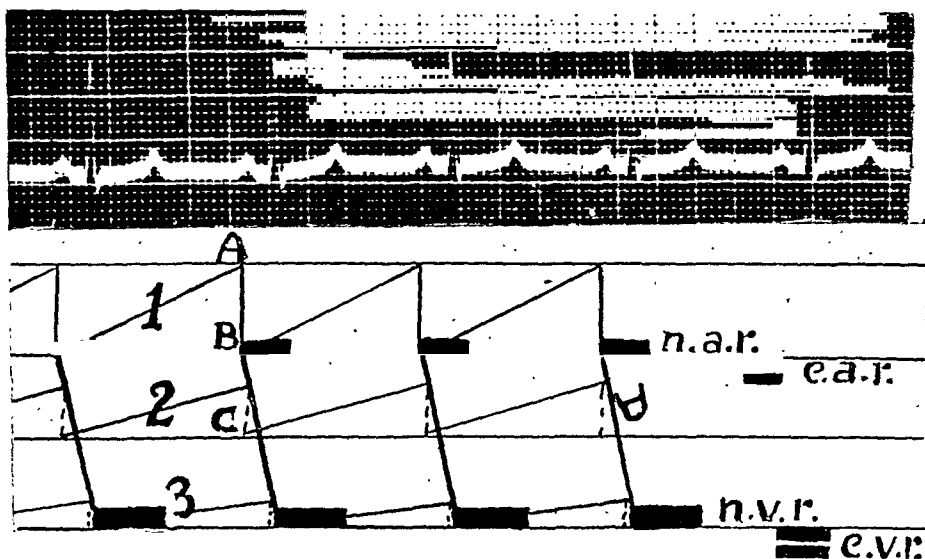


FIG. 1.—Normal sinus rhythm.

To facilitate in the discussion of the electrocardiograms a uniform graphic illustration of the mechanism is included under each figure. The general scheme is shown in Figure 1 which diagrammatically illustrates the mechanism in normal sinus rhythm. Lines 1, 2, and 3, represent impulse formation in the three rhythmic centers—the sinoauricular, auriculoventricular and ventricular centers respectively. It is assumed that the three centers are building stimuli simultaneously. Horizontal lines A, B, and C, represent the height to which these impulses must be raised before they attain effectiveness. The sinoauricular node is represented as developing stimuli most rapidly. The auricular response is represented by the solid upper rectangle (n.a.r.). The line D, joining the two rectangles represents the duration of excitation in the auricle and of conduction to the ventricle.\*

\* This is not entirely true to fact insofar as the string does not deflect until a sufficient mass of muscle has been activated.



The lower rectangle (n.v.r.) represents a normal ventricular response. As the excitation wave spreads over the two lower centers it discharges the impulses forming in them before they have reached effectiveness.<sup>1</sup> The width of the rectangle represents the refractory period. In succeeding electrocardiograms impulse formation in an ectopic center will be represented by an ascending broken line. Ectopic auricular and ventricular responses will be shown by horizontal bars below the second (e.a.r.) and lowest lines (e.v.r.) respectively.

The illustrations that follow will be presented along the plan of the outline. Figures 2 to 10 show rhythms occurring when the conducting tissue is normal and is capable of transmitting impulses from auricle to ventricle, but not from ventricle to auricle. (Unidirectional retrograde block), Group I.

Figure 2 illustrates isolated *A-V* nodal escape—when the sinus is depressed by pressure over the eyeball. (In the Table 1 *A 2a*). When the sinus node is sufficiently slowed, as occurs after the second cycle, a complex arising from an *A-V* nodal center appears. No inverted auricular complexes are seen and it must be assumed that the impulse is not conducted from the lower center and that retrograde conduction is blocked. There is a long period of cardiac standstill. This would indicate that the *A-V* node as well as the *S-A* node were depressed—but that the *A-V* node recovered first. Another interpretation might be that the *S-A* node alone was depressed and that the gradual quickening of the *A-V* nodal rhythm represents "rhythm of development."<sup>4</sup> Toward the end of the figure the sinus node recovers from vagus influence and resumes cardiac control.

Figure 3 illustrates escape of an ectopic ventricular center (Group Ib 1.) The isolated ectopic ventricular beats shown are not succeeded by an abnormal auricular complex indicating that the impulses from the ventricle are not conducted backward. The ventricular complex is abnormal and appears consistently whenever the *S-A* node is slowed to a cycle length of 1.3 seconds. This was true for a long strip of electrocardiogram in which many escaped beats appeared. It is of interest to point out that the *R-R* intervals preceding ectopic beats are always equal. This seems to indicate that the slow ectopic center is continuously active but is submerged by the slightly more rapid auricular pacemaker. When the latter slows sufficiently the submerged center develops an effective stimulus and escapes from auricular control. Here as in the previous example the depressant factor seems to act only or predominantly upon the sinus node—allowing for escape of lower centers.

The preceding electrocardiograms are examples of isolated escaped beats of a lower center when the sinus is depressed. This mechanism is considerably less common than that in which the rate of the sinus remains unchanged while a dormant rapid center

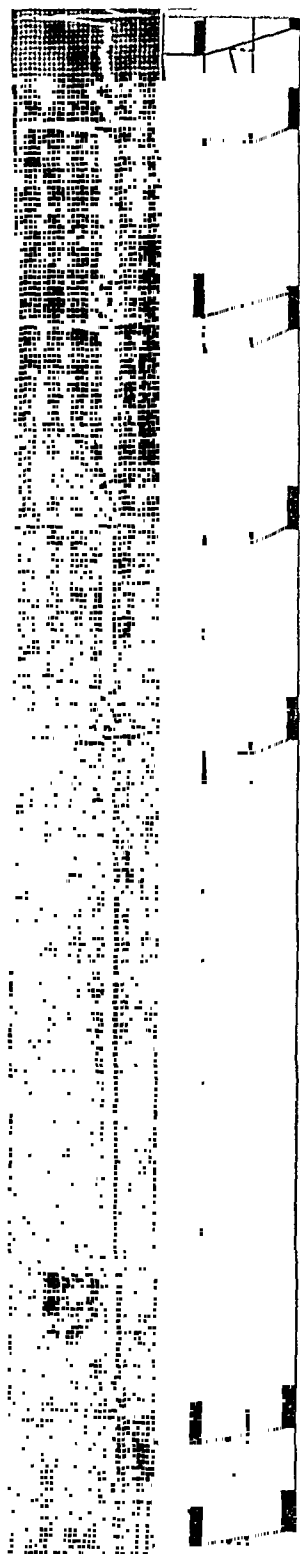


FIG. 2.—A-V junctional escape.

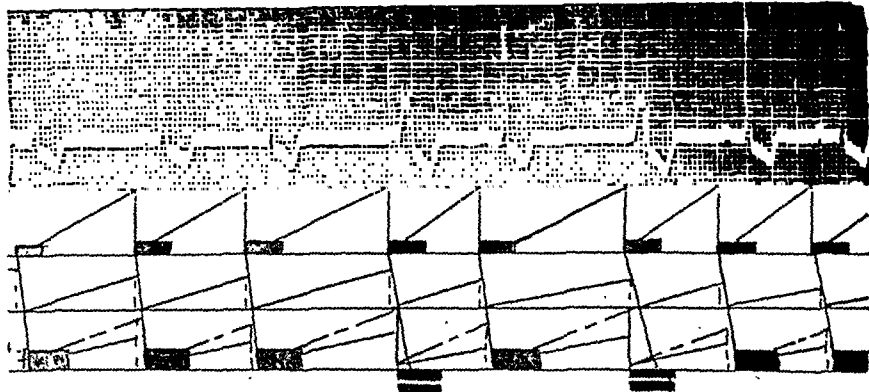
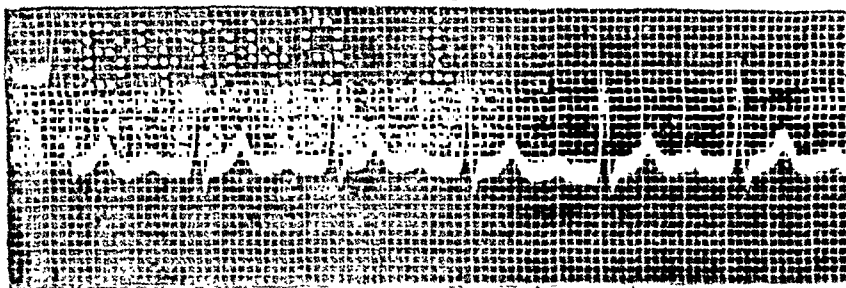
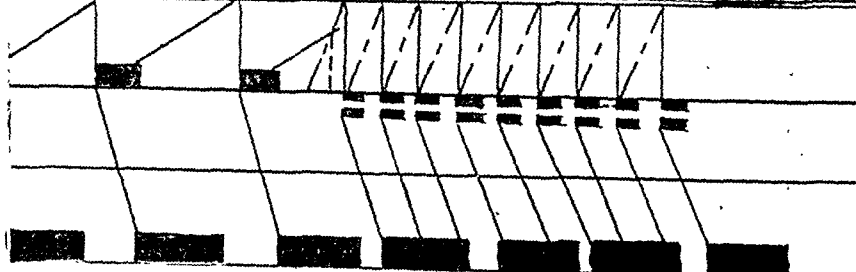
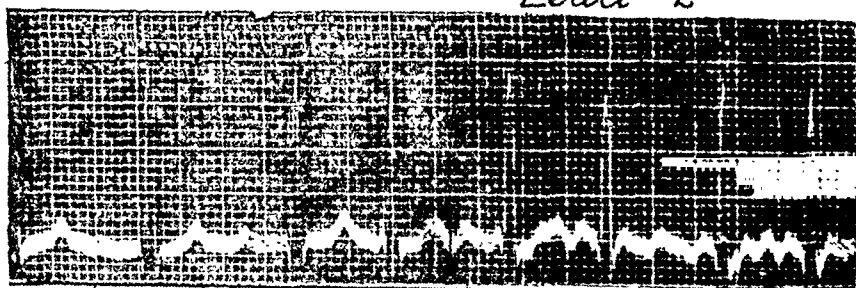


FIG. 3.—Ectopic ventricular escape.

*Lead 1*



*Lead 2*



*Lead 3*

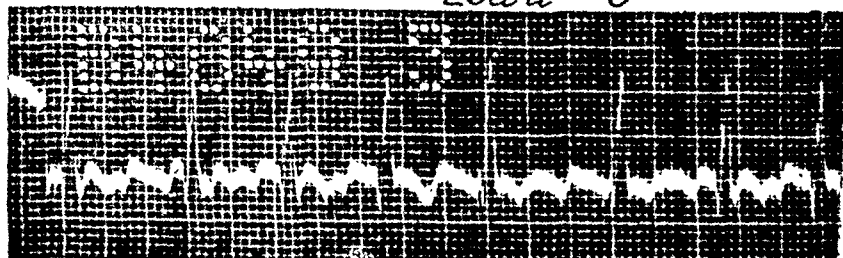


FIG. 4.—Transition from sinus rhythm to auricular flutter.

is stimulated to activity. Premature contractions and the various tachycardias are familiar examples. Most common are the rhythms originating in the auricle—auricular premature contractions, and the various auricular tachycardias. These are too familiar to need repetition. One interesting case of this type will be shown because the electrocardiogram shows a transition from one rhythm to another.

Figure 4 illustrates dormant flutter rhythm spontaneously stimulated to activity (Group 1A 4). The transition appears in Lead II. This case is included in the group of unidirectional retrograde block because of the following reasons: The flutter cycle lengths are 0.21 second. This would indicate that the auricular refractory period is equal to or less than 0.21 second. During sinus rhythm the *P-R* interval is 0.24 second. Ventricular excitation begins, therefore, 0.03 second after the auricle has passed out of its refractory period.

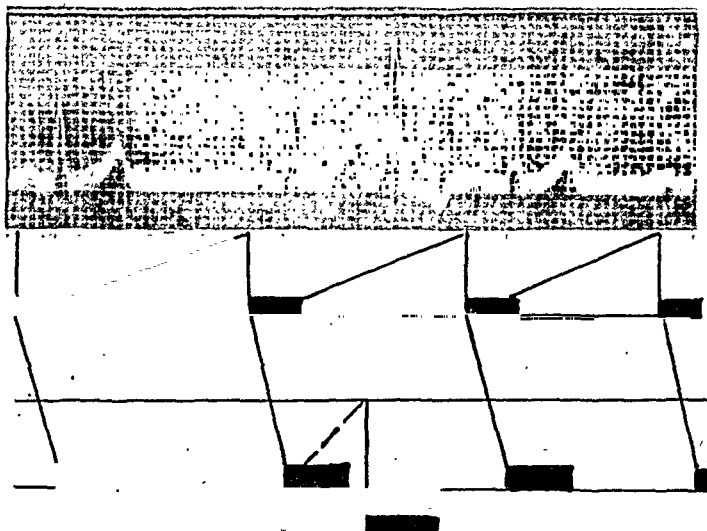


FIG. 5.—Premature ventricular contraction (interpolated).

If the ventricular impulse were conducted to the auricle it would reënter that chamber after its refractory period and elicit an auricular response—"reciprocal beat."<sup>3</sup> To explain the absence of retrograde auricular response it must be assumed that the impulses are blocked and that retrograde conduction is impaired.

Rapid dormant centers of the ventricle are rarely stimulated to continuous activity though they frequently dominate isolated cardiac cycles—premature ventricular contractions are familiar examples, and need no illustrations. It is worth pointing out, however, that when a ventricular premature beat appears it is extremely rare to see it followed by a retrograde auricular response. This is

not because the retrograde impulse reaches a refractory auricle, for when a premature ventricular contraction appears very early in diastole, such as occurs when the beat is interpolated, the auricle still continues to respond to its own center. This indicates that normally retrograde conduction is impaired. Figure 5 shows an interpolated ventricular premature contraction and demonstrates that phenomenon. Premature ventricular excitation occurs when the auricle is out of its refractory phase—but no retrograde auricular response follows. It must be assumed that the ventricular impulses are blocked and the retrograde conduction is impaired. This arrhythmia fits into Group IB 3.

Figures 6 to 9 are rare arrhythmias—showing continuous activity of low rapid centers.

In all of these the conducting mechanism fits into the classification of unidirectional block with retrograde conduction impaired (Group I).

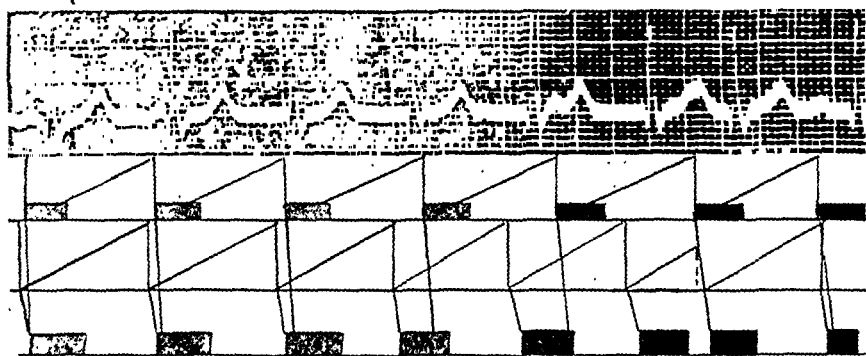


FIG. 6.—Independent rhythm with retrograde block. Auricle controlled by sinus node; ventricle controlled by *A-V* node.

Figure 6 is a paroxysm of rapid rhythm, either of the *A-V* nodal or idioventricular centers (Group IA 2*d*). The auricles and ventricles are controlled by independent centers, the auricle by the sinus node, the ventricle by the lower center. This type of arrhythmia has appeared in the literature as complete heart block.<sup>5</sup> This is a mistaken interpretation because the conducting mechanism is normal. It will be noted that the ventricular rate is slightly higher than the auricular, the ventricular cycle length is 0.66, and the auricular cycle length is 0.70 second. The evidence against complete heart block and in favor of normal auriculoventricular conduction is revealed by complex 7. This complex is in response to a supraventricular impulse and appears as a premature beat succeeding an auricular complex which superimposes the *T* wave. In the entire curve wherever this relationship of *P* and *T* existed the succeeding ventricular complex was premature (parasystole).<sup>6</sup> This premature beat represents a response to a normally conducted sinus stimulus which reached

the ventricle after it had passed out of its refractory state. Succeeding sinus impulses, however, are anticipated by those from the more rapid *A-V* node which again takes up the rhythm of the ventricle. This continues until another sinus stimulus opportunely placed elicits a ventricular response. The two independent rhythms continue with periodic sinus control of both chambers. This can be possible only if conduction from auricle to ventricle is intact and retrograde conduction impaired.

Figure 7 is another example of the same mechanism and illustrates the conditions in most of the ventricular tachycardias (Group Ib 4). The center controlling the ventricle is below the bifurcation of the conducting tissue. It displaces the slower impulses from the auricle and controls the ventricle. The rapid impulses are not conducted backward to the auricle which continues to respond to the slower sinus node. It will be noted that after the second and

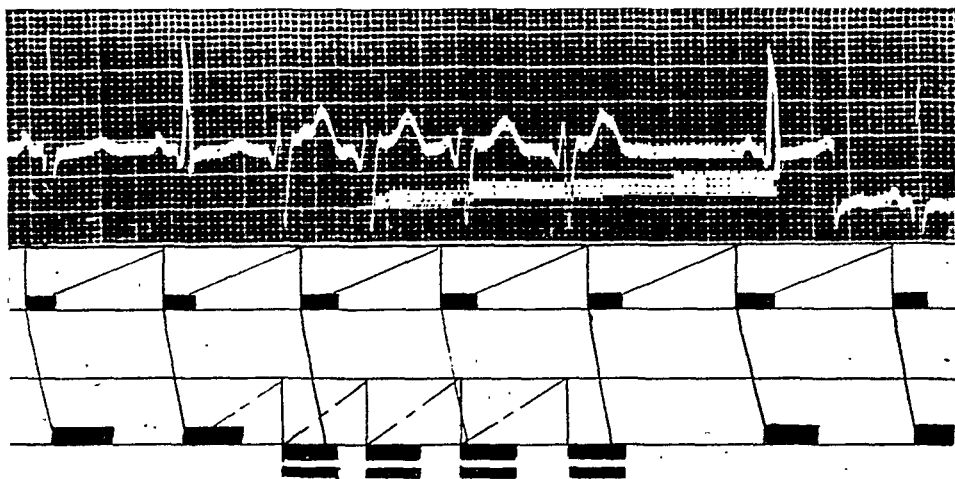


FIG. 7.—Ventricular rhythm with retrograde block.

possibly also after the third ectopic beat a retrograde impulse would have reached the auricle considerably after its excitation phase and most probably after its refractory period. It is difficult to explain the absence of a retrograde auricular response on the basis that the retrograde impulse falls on a refractory auricle. One must rely on the explanation that the ventricular impulses are not conducted to the auricle and that retrograde block exists.

Arrhythmias of the same type are illustrated in Figs. 8 and 9. The former was produced by pressure over the precordium.<sup>7</sup> That in Fig. 8 occurred spontaneously. They are present as additional examples of Group Ib 4 because of their unusual interest. In both arrhythmias sinus control of the ventricle is replaced by a more rapid center probably very near the bifurcation of the His bundle. These impulses are not conducted to the auricle and the sinus retains control of that chamber.

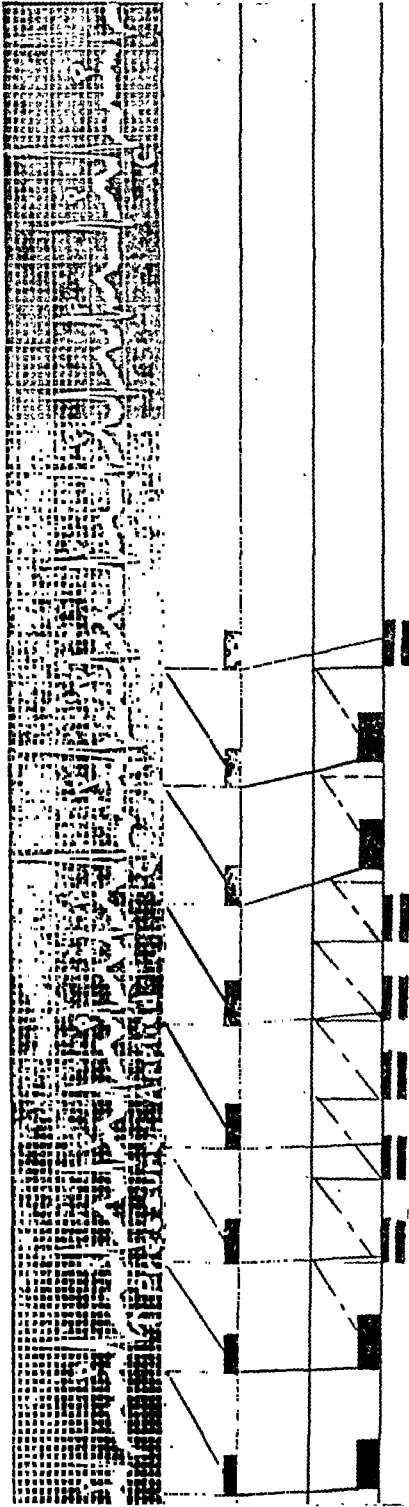


FIG. 8.—Independent rhythm with unidirectional block.

In these tracings, as in Fig 6, when an auricular impulse is so placed that it reaches the ventricle after its refractory phase and before the ectopic center has had time to develop an effective impulse the ventricle responds to the sinus node. This occurs wherever an auricular complex is superimposed on a *T* wave. The succeeding ventricular response is premature and a parasystole appears. This and the following ventricular complexes are the result of supra-ventricular stimulations. The third sinus impulse, however, is anticipated by a stimulus from the more rapid ectopic center and falls upon a refractory ventricle. The auricular rhythm continues

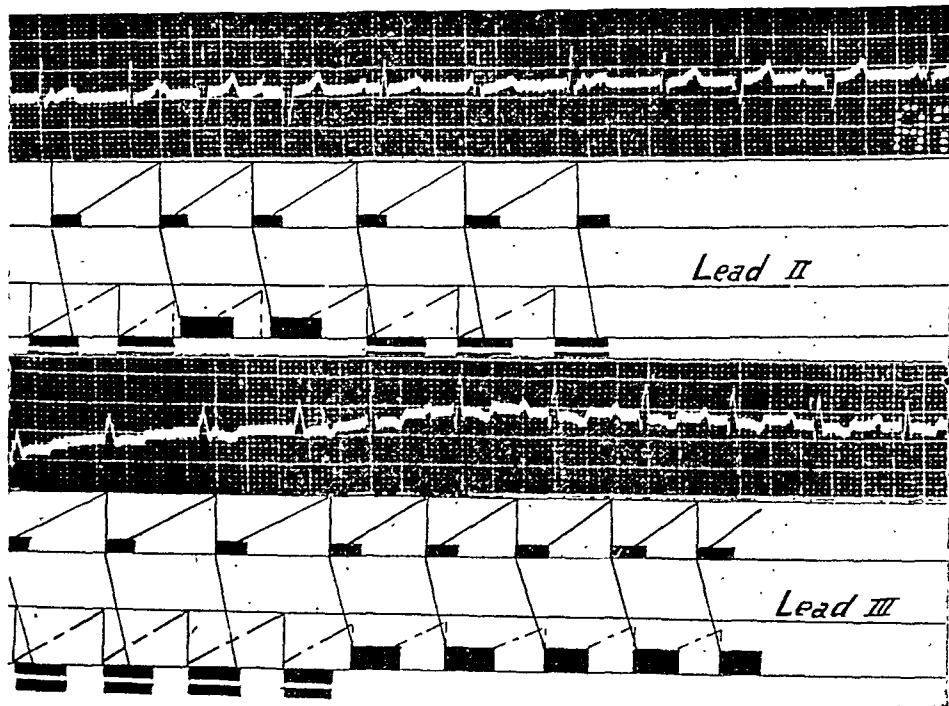


FIG. 9.—Transition from independent rhythm with unidirectional block to sinus rhythm.

undisturbed; the ventricular rhythm is periodically interrupted by premature beats (parasystoles). In Lead III of Fig. 8 the sinus regains control of the whole heart when its rate of stimulus production spontaneously increases to exceed the lower center. When the ectopic center dominates the ventricle the ventricular rate is 83 per minute, the auricular rate is 79. After the fourth ventricular complex the sinus node spontaneously accelerates to 86 per minute and regains control of the entire heart.

Figures 10 to 13 are illustrations in which the conducting tissue transmits impulses in either direction (Group II). Examples of that mechanism are rare but are not infrequently seen in cases where the dominating center is above the bifurcation of the bundle



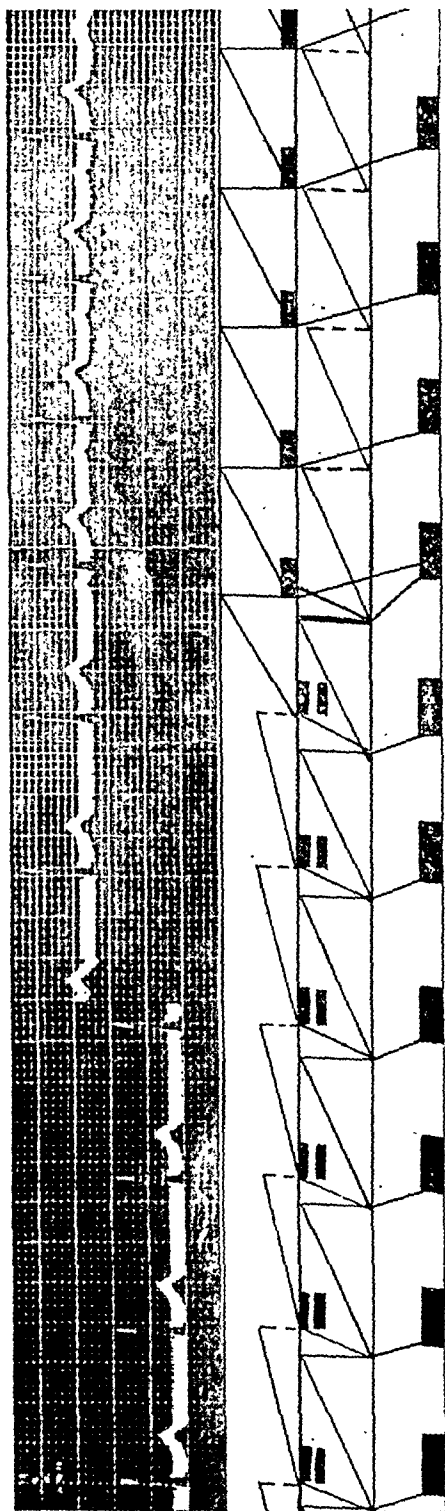


FIG. 10.—Transition from 4-V nodal rhythm with retrograde conduction to sinus rhythm.

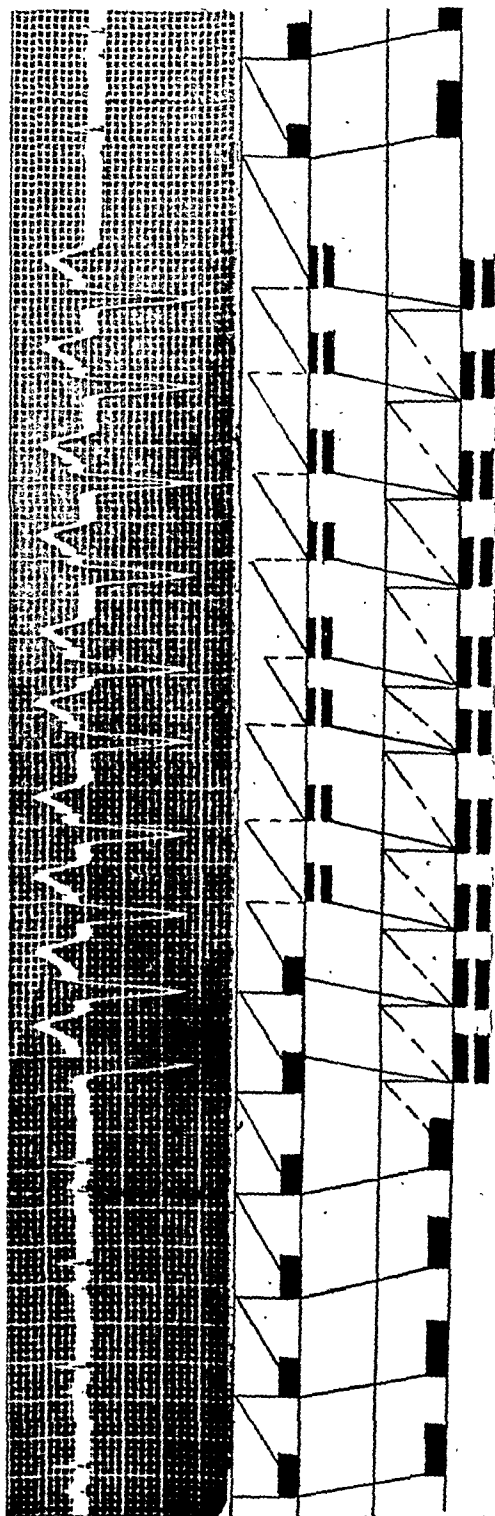


FIG. 11.—Ventricular tachycardia with retrograde conduction.

tissue. Such rhythms probably have their origin in the *A-V* node and the auricular response is in effect due to aberrant excitation from an abnormal auricular focus, rather than to a retrograde ventricular impulse. It is extremely rare to see examples in which the center of cardiac control is below the division of the bundle of His.

Figure 10 shows a paroxysm of low nodal rhythm (Group IIA 2d). The center dominates the entire heart, its impulses spreading downward to the ventricle and upward to the auricle. The sequence of contraction is reversed—the auricular complex appears upon and after the down stroke of the *R* wave. *A-V* nodal rhythm at a rate of 79 per minute continues through the 6th complex. At that point the sinus node accelerates its own rate to 86 per minute, regaining cardiac control. This, and the previous figure, illustrate that the most rapid center is dominant in the cardiac chamber in which it exists. It will control the entire heart if its impulses are conducted to the other chamber.

Figure 11 is an unusual example of complete cardiac control by a rapid ectopic ventricular center (Group IIB 4). Apparently retrograde conduction is unimpaired and equal to or closely equal to forward conduction. This is evidenced by the fact that the *P-R* and *R-P* intervals differ by 0.02 second. Impulses from the ventricle spread upward and replace the slower sinus node. The retrograde auricular response does not appear in the first two ectopic ventricular complexes because the retrograde impulse finds the auricle refractory.

Figure 12 is another very rare illustration of retrograde conduction and rhythm control by a lower ectopic center (Group in IIB 2). Here, however, ventricular control is affected by the depression of the sinoauricular node in a phasic arrhythmia, allowing for escape of a comparatively slow ectopic center. Occasionally the ventricle is stimulated simultaneously by an impulse from the auricle and by one from the ectopic center. When that occurs a "transition"<sup>8</sup> complex appears. Such is the interpretation given the last aberrant complex. When the rate of stimulus production in the sinus speeds up, as occurs at the end of the paroxysm, control of the rhythm reverts to the natural pacemaker. The interplay of these two centers continued over a long tracing in which one or the other gained control depending upon the rate at which the sinoauricular node builds up its impulses. Impulse formation in the ectopic center remained constant, cycle length 0.86 second, whereas the sinus cycle length varied between 0.75 and 0.96 second. The inverted deflections terminating aberrant *R* 2-6 are interpreted as retrograde auricular complexes. Where they fail to appear at the beginning and end of the paroxysm they do so because the auricle has responded to the sinus and is refractory to the retrograde impulses from the ventricle.

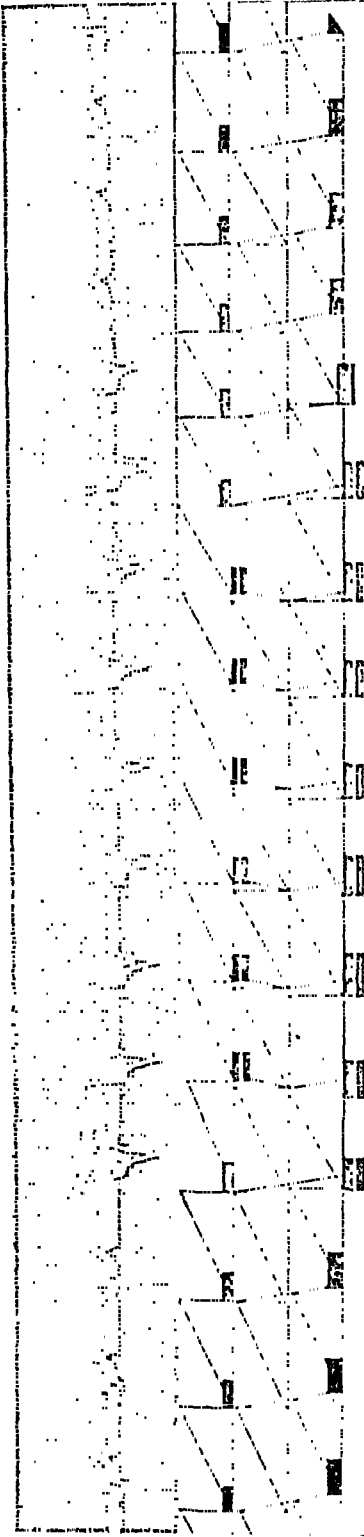


Fig. 12.—Escaped ventricular rhythm with retrograde conduction.

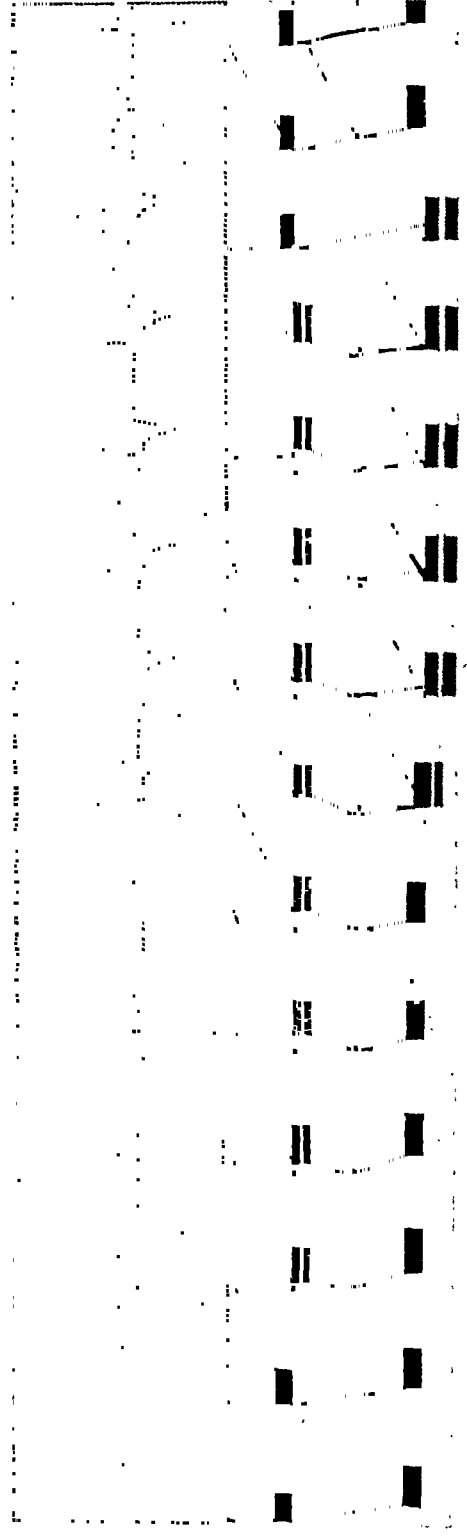


Fig. 13.—Escaped nodal and ventricular rhythm with retrograde conduction.

There is the possibility that these inverted complexes are retrograde from the node and not from the ventricle. If such is the mechanism the tracing illustrates independent rhythms in which the auricle is responding to the *A-V* node and the ventricle to an ectopic center. Figure 13 seems to support that interpretation. It is another paroxysm in the same patient. The first two ventricular complexes are of sinus origin; complexes 3 to 6 are of nodal and 7 is transitional. These are followed by a paroxysm of ectopic rhythm. The 3d and 4th auricular complexes are probably also transitional representing a response to impulses from the *S-A* and *A-V* nodes. It will be noted that the auricular complexes gradually shift from a position in front of the ventricular complex to one following and again to appear in its natural sequence when the sinus regains control. The absence of fixed relationship to the abnormal ventricular complex suggests that the auricle is beating independently. Another point which favors that interpretation is the fact that the *P-R* interval of the normal cycle exceeds the *R-P* interval of the ectopic cycle. One would have to assume the unlikely possibility that retrograde conduction is more rapid than forward. The fact that the auricular complexes are abnormal and at times inverted favors the *A-V* node as the pacemaker of the upper chamber. The manner in which the abnormal *P* waves shift into and then follow the *Q-R-S* complexes suggest the possibility that the site of impulse initiation in the node may be at several levels.<sup>9</sup>

In this tracing the depressor effect in a sinus arrhythmia is felt first by the sinoauricular node. When the latter is sufficiently slowed the *A-V* node escapes. Finally an ectopic ventricular center takes up the rhythm. It is not clear why the ventricular center did not submerge the *A-V* node from the start for the rate of the former is slightly higher. A possible explanation may be that the rapid auricular impulses not only submerges but depresses the ventricular center.<sup>4</sup> As the supraventricular impulses decrease in frequency the ventricular center accelerates its own rhythm until it escapes from supraventricular control.

In complete heart block (Group III) the chambers are independent and each has its own center of impulse formation. In the usual examples the sinus node controls the auricle and a center of slow rate situated above or below the bifurcation of the His bundle controls the ventricle. Ectopic centers may replace these and the usual relationship of auricular and ventricular rates may be reversed. Levine and Matton<sup>10</sup> published a remarkable case in which the ventricular rhythm either was or closely bordered upon ventricular fibrillation. In a case of complete heart block published by Kerr and Bender<sup>11</sup> both auricles and ventricles are fibrillating.

Figure 14 is an example of complete heart block in which the auricle is fibrillating and the ventricle is responding to its own rhythmic center, Group IIIA5 B2. Two reasons are offered for the

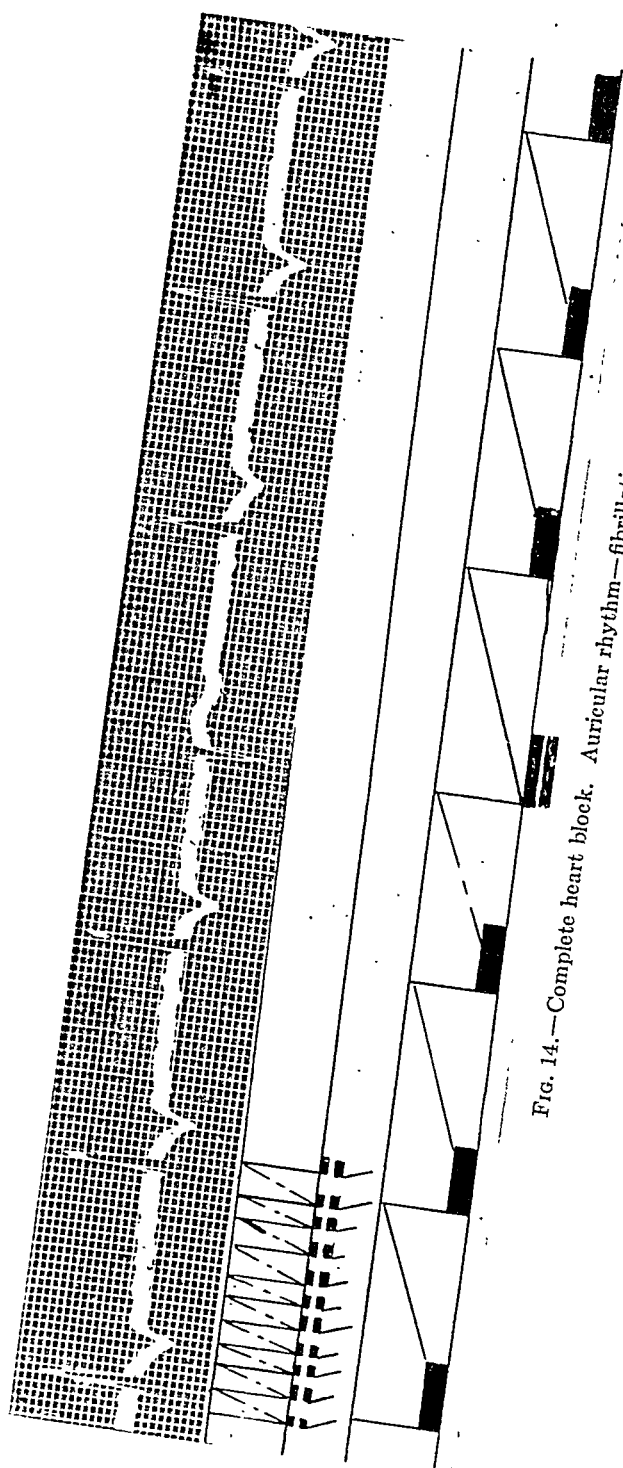


Fig. 14.—Complete heart block. Auricular rhythm—fibrillation.

interpretation here of complete heart block. First is the regularity of the ventricle cycle lengths which are 1.02 second. The second is the effect of a premature beat on this regularity. It will be observed that the interval succeeding the premature beat is exactly equal to the interval between two regular ventricular complexes. Such premature beats appeared frequently and in each instance the succeeding interval measured 1.02 second. This relationship is evidence against auricular control of the ventricle, for if the latter were the case, premature contractions of the ventricle could not interfere with the impulses from the fibrillating auricle except for the short period of refractoriness, and the succeeding intervals would vary dependent only upon the arrival of an effective auricular stimulus. Thus complete heart block best explains the mechanism in this tracing. The auricle is responding to a circus movement and the ventricle to an independent ventricular center which emits stimuli at regular intervals. When a premature extraneous impulse spreads through the ventricle it discharges the stimulus forming in the regular center and the latter must initiate a new impulse. The rate at which it develops impulses remaining constant it follows that the cycle length succeeding a premature contraction should be equal to that between two regular complexes.

**Summary.** Human electrocardiograms are described which illustrate the mechanism of the control of cardiac rhythm. They support the theory that the heart responds to the rhythm center which develops effective stimuli most rapidly. It is shown that a submerged slower center can gain control when its rate in relation to the others changes so that it becomes the most rapid. This is effected either by stimulation of the submerged center or depression of the dominating center.

The effect of the state of conduction on cardiac rhythm is shown and discussed.

Evidence for simultaneous activity of several centers is illustrated.

The following rare clinical examples of cardiac arrhythmia are shown:

1. Escape of an ectopic ventricular beat.
2. Escape of slow ventricular ectopic rhythm.
3. Transition from nodal rhythm to sinoauricular rhythm.
4. Transition from ectopic ventricular rhythm to sinus rhythm.
5. Transition from sinus rhythm to auricular flutter.
6. Retrograde conduction.
7. Unidirectional block.
8. Parasystole.
9. Complete heart block with auricular fibrillation.

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## LEFT AXIS DEVIATION WITH AND WITHOUT HEART DISEASE.\*

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IN a study of the electrocardiogram in patients with obesity<sup>1</sup> it was observed that left axis deviation in the presence of an erect *T* wave in Lead III was generally found in patients with objective evidence of heart disease. When the *T* wave in Lead III was inverted the left axis deviation was found usually to be due simply to a change in the position of the heart. A further analysis of the significance of various associated features in the presence of left axis deviation indicated that in addition to the erect *T* wave in Lead III, a relatively low *T* wave in Lead I and a deep *S* wave in Lead II also were frequently found in the presence of heart disease.<sup>2,3</sup> In the present study, an attempt is made further to establish the clinical significance of these findings associated with left axis deviation.

One hundred and thirty-six electrocardiograms with left axis

\* This study was made possible by a grant from the Bingham Associates Fund.

deviation were analyzed. In all cases the electrical angle calculated from the electrocardiogram, according to Einthoven, was less than 20 degrees.

Those patients were considered to have normal hearts in whom there was no clinical or roentgenologic evidence of heart disease and in whom the blood pressure was normal. The abnormal clinical cases were those in which there was either definite roentgenologic evidence of cardiac enlargement, a persistent elevation of the systolic blood pressure over 170 mm. Hg, or both. In the few questionable cases the systolic blood pressure was between 150 and 170 mm. Hg, with or without probable slight cardiac enlargement.

The attempt was chiefly to determine the significance of the presence or absence of the following: A low erect *T* wave in Lead I, the *T* wave being less than one-seventh of the amplitude of the *R* wave, an *S* wave in Lead II of at least one-half the amplitude of the *R* wave and an erect *T* wave in Lead III. Those cases were regarded as simple left axis deviation in which none of these findings were associated. Others were classified according to whether they showed one, two or all of the above signs. Aside from the left axis deviation and the findings above referred to, which in themselves are not indicative of heart disease, the electrocardiograms showed no abnormalities.

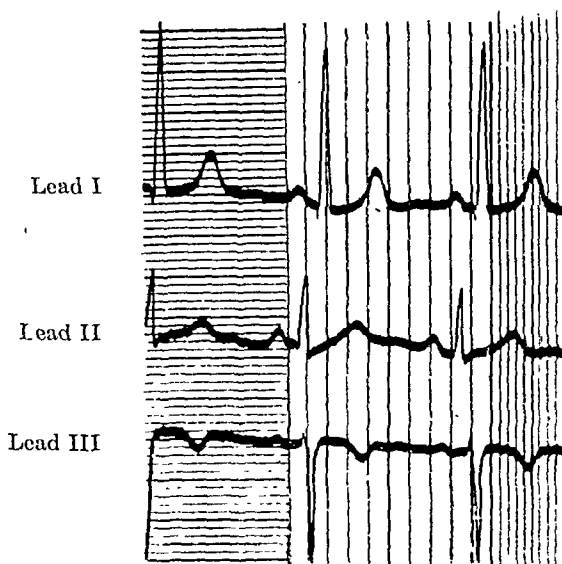


FIG. 1.—Left axis deviation of the type associated simply with change in the position of the heart. Note the relatively high *T* wave in Lead I, the absence of an *S* wave in Lead II and the inverted *T* wave in Lead III.

**Results.** *Left Axis Deviation With No Significant Changes* (Fig. 1). There were 24 cases of left axis deviation in which the *T* wave in Lead I was erect and prominent, the *T* wave in Lead III inverted



and the *S* wave in Lead II either absent or insignificant. In these 24 cases there was definite evidence of heart disease in only 2 and questionable evidence in 2.

In an evaluation of electrocardiograms from material such as we are analyzing, it is obvious that in a certain percentage of cases in which the electrocardiograms are entirely normal, there will be definite cardiac disease—first because most of the patients on whom electrocardiograms are obtained either have or are suspected of having heart disease and second because not infrequently even in the presence of advanced cardiac disease the electrocardiogram may be normal. The incidence of cases in which there was objective evidence of heart disease in the presence of a normal electrocardiogram was found to be 38% in 100 consecutive cases. In other words, slightly more than one-third of our normal electrocardiograms are found in patients with heart disease.

On the other hand, in only 17% (4 out of 24) of the cases of what we considered simple or insignificant left axis deviation was there evidence of heart disease. This unusually low incidence is due to the fact that a large number of these electrocardiograms were taken in cases of simple obesity. In the non-obese cases the incidence of cardiovascular abnormality in the presence of what is considered simple left axis deviation was 33%, which corresponds closely to the incidence of diseased hearts in the control series of normal electrocardiograms.

*Left Axis Deviation With Significant Change in Only One Lead.* There were 38 cases of left axis deviation in which only one of the signs above referred to was present, with definite evidence of cardiovascular disease in 27 (71%). In these 27 cases the significant change associated with the left axis deviation was a deep *S* wave in Lead II in 16 cases, an erect *T* wave in Lead III in 10 cases and a low *T* wave in Lead I in only 1 case. This 71% is contrasted with the 38% of normal electrocardiograms found in the presence of heart disease in the control group.

In the remaining 11 of the 38 cases in this group, 7 had no evidence and 4 only questionable evidence of heart disease. Of the 7 patients with no evidence of heart disease, 4 had a deep *S* wave in Lead II, and 3 in an erect *T* wave in Lead III; while of the 4 cases with questionable evidence of heart disease, 3 showed a deep *S* wave in Lead II and 1 an erect *T* wave in Lead III.

*Left Axis Deviation With Significant Changes in Two Leads.* There were 34 electrocardiograms showing left axis deviation in the presence of significant changes in at least two leads. In 27 (79%) of these cases there were objective signs of cardiovascular damage. In these cases no one grouping of associated electrocardiographic changes was considerably more frequent than another. In 9 of these cases the changes were in the *T* waves in Leads I and III; in 10 cases the changes were in the *S* wave in Lead II and the *T*

wave in Lead III, and in 8 cases the changes were in the *T* wave in Lead I and the *S* wave in Lead II. Of the 7 cases in this group in which the blood pressure and heart were normal the electrocardiographic changes were found in the *S* wave in Lead II and the *T* wave in Lead III in 6, and in the *T* wave in Lead I and *S* wave in Lead II in the remaining case.

*Left Axis Deviation With Significant Changes in All Leads* (Fig. 2). There were 40 cases of left axis deviation in which changes were observed in all leads. In 38 (95%) there was obvious cardiovascular disease. This incidence of disease is sufficiently striking to warrant considering such electrocardiograms regularly as distinctly abnormal.

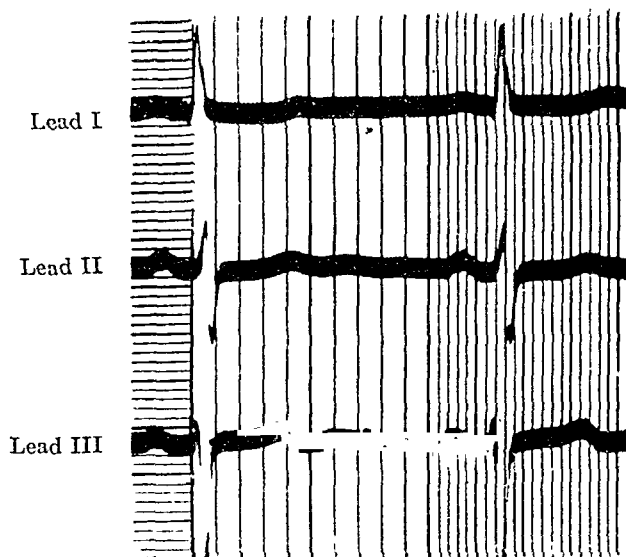


FIG. 2.—Left axis deviation of the type generally associated with myocardial disease. Note the relatively low *T* wave in Lead I, the prominent *S* wave in Lead II and the erect *T* wave in Lead III.

*Results of Follow-up Studies.* In 28 cases we were able to obtain two or more electrocardiographic records over periods varying from 7 months to 4 years. Of these 28 cases, 22 had evidence of heart disease; 13 of the 22 showed progressive changes of one type or another. There was nothing in their clinical course to indicate that the progressive changes in the electrocardiograms might have been due to coronary occlusion nor could the changes be attributed to digitalis effect. In 6 of the 22 cases initial changes were present in all three leads. In all of these cases the *T* wave in Lead I became lower (to the point of inversion in 1 case), while in 5 of the cases the *T* wave in Lead III became more positive and in 1 the *S* wave in Lead II became deeper. In a study of progressive myocardial disease, Willius<sup>4</sup> illustrates the development of an inverted *T* wave in Lead I in 9 months in a patient whose initial electrocardiogram,

considered "essentially normal," showed left axis deviation with the changes in the three leads above described.

In 7 cases in which there were initially a low *T* wave in Lead I and an erect *T* wave in Lead III, the *T* wave in Lead III became

A

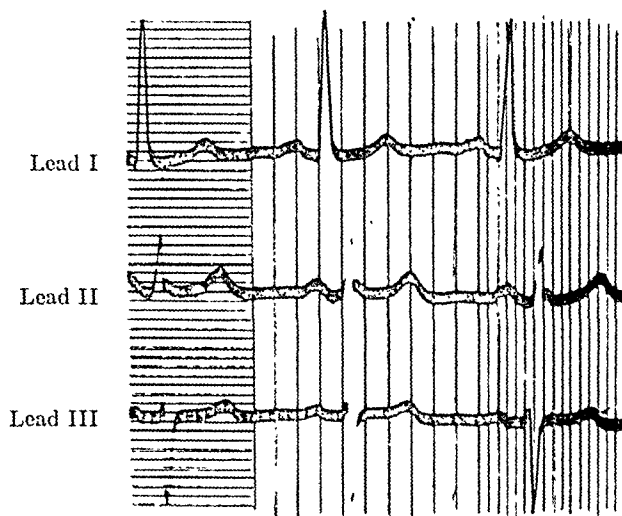


FIG. 3 A.—Left axis deviation with a relatively low *T* wave in Lead I and an erect *T* wave in Lead III in the presence of hypertensive heart disease with moderate cardiac enlargement.

B

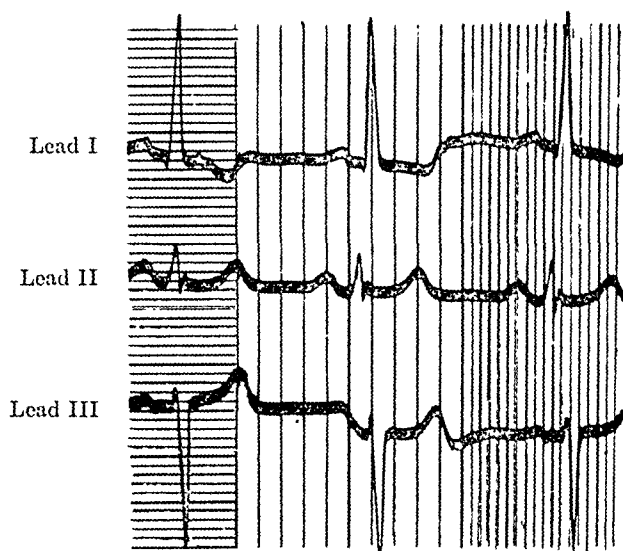


FIG. 3 B.—An electrocardiogram taken 19 months later on the same patient, showing the development of an inverted *T* wave in Lead I, a slight *S* wave in Lead II and a more prominently erect *T* wave in Lead III.

more positive in 4 cases while the *T* wave in Lead I became lower, in 1 case actually becoming negative (Fig. 3). In the remaining 3 of these 7 the *S* wave in Lead II became deeper. Nine of the 22 cases which had evidence of heart disease showed no change on successive electrocardiograms. Of these 9, 2 had initially what we termed "simple left axis deviation;" 1 had only a deep *S* wave in Lead II, 2 showed changes in the *T* wave in Lead I and the *T* wave in Lead III, and 4 showed changes in all leads.

In 6 of the total 28 cases in which repeated electrocardiograms were observed there was no evidence of heart disease nor were there any significant changes associated with the left axis deviation. In these cases, over a period of 3 to 4 years, no progressive changes were observed in the electrocardiograms.

**Discussion.** In 1921, Herrmann and Wilson<sup>5</sup> observed that while rotation of the heart produced in the *P* and *T* waves changes similar to those which it produced in the *Q-R-S* waves, ventricular preponderance did not affect *P* waves and its effect upon *T* waves was uncertain. Cohn and Raisbeck<sup>6</sup> concluded similarly, in regard to the *Q-R-S* and *T* wave relationship, that the form and direction of the *T* wave in preponderance curves of enlarged hearts did not change in so simple a manner on rotating leads on the chest wall (thus simulating the change in position of the heart in the chest wall) as was the case in a normal subject. They thought this was perhaps because the *T* waves in the first place were not so prominently and in the second place not so simply formed. Bland and White<sup>7</sup> noted that a total inversion of Lead III was usually associated simply with change in the position of the heart. While this is true of total inversion, it appears likewise to be true of inversion only of the *Q-R-S* and *T* waves.<sup>1</sup>

There is, therefore, adequate evidence to indicate that when the *Q-R-S* and *T* waves behave uniformly as the electrical axis changes, the change in axis is due simply to change in the position of the heart. This appears to be true not only of the *Q-R-S-T* wave relationship in Lead III but in Lead I as well.<sup>2</sup>

In the presence of myocardial disease, however, there is a disturbance in the *Q-R-S-T* relationship manifested chiefly by a tendency for the *T* wave to assume a direction opposite to that of the initial ventricular complex.<sup>2,8</sup> Probably this is in some way associated with a disturbance in conduction of the ventricular muscle, a disturbance in the pathway of retreat. (The tendency of the initial and final ventricular phases to assume opposite directions in the presence of conduction disturbance in one of the bundle branches is associated with a spreading of the initial complex and is probably not directly related to the mechanism here referred to.) We should anticipate, therefore, in the presence of left axis deviation with myocardial disease that the *T* wave in Lead I would either fail to increase in amplitude or would actually decrease as the *R* wave

in Lead I becomes more positive, also that the *T* wave in Lead III would fail to become negative or actually would become more positive as the *Q-R-S* wave in Lead III becomes more negative. Such a disturbance in the behavior of the two phases of the ventricular complex in the presence of left axis deviation would seem to have the same significance as the development of an inverted *T* wave in Lead I, for example, which likewise represents simply a disturbance in the normal *Q-R-S-T* relationship and is generally thought to be due to myocardial damage, though Barnes and Whitten<sup>9</sup> might account for such a change as well as the progressive changes above described as due probably to a progressive hypertrophy of the left ventricle. It is, however, reasonable to assume that where there is a relatively low *T* wave in Lead I and an erect *T* wave in Lead III in the presence of left axis deviation of the *Q-R-S* wave there is evidence of myocardial change, either hypertrophy or some other form of disease.

Just what the significance of the prominent *S* wave in Lead II is in this connection we are not prepared to say. It appears to be in some way associated with cardiac abnormalities in the same manner as the *T*-wave disturbances above referred to. Wilson, Macleod, Barker, Johnston and Klostermeyer,<sup>10</sup> later Winternitz,<sup>11</sup> reported changes in the initial deflection of the ventricular complex in myocardial infarction. Perhaps the change in *S* wave in Lead II here described bears the same relation to such changes as Wilson and his coworkers reported (more particularly the "*Q*<sub>1</sub>" type) as the slowly developing, roundly inverted *T* wave bears to the characteristic rapidly developing sharply inverted *T* waves in the presence of acute infarction. In 1 case the myocardial changes develop relatively rapidly; in the other slowly. In both cases, however, the electrocardiographic changes signify myocardial disease.

**Summary.** 1. Electrocardiograms showing left axis deviation with no other abnormal findings were analyzed with particular reference to the presence or absence of a relatively low erect *T* wave in Lead I, a prominent *S* wave in Lead II and an erect *T* wave in Lead III.

2. The analysis indicates that in the absence of any of the three changes above enumerated the left axis deviation is not associated with cardiovascular disease. In the presence of one of the changes the incidence of associated cardiovascular disease is considerable, in the presence of two changes it is greater, while the presence of all three changes constitutes almost invariable evidence of heart disease.

3. Observations of repeated electrocardiograms taken over periods varying from 7 months to 4 years show the development of these associated changes in the presence of progressive cardiovascular disease.

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## ELECTROCARDIOGRAPHIC CHANGES FOLLOWING THE ADMINISTRATION OF POTASSIUM IODID IN SYPHILITIC HEART DISEASE.

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THIS case is presented as evidence of marked change taking place in the syphilitic heart, following the administration of potassium iodid, even in comparatively small doses.

**Case Report.** The patient, a man aged 55, when first seen on February 1, 1934, complained of shortness of breath. This condition was noticed some 3 months before, when climbing stairs. At that time he was given "green drops" by his physician and felt better within a week. He returned to work and had no further trouble until the week preceding the present visit, when he began to experience shortness of breath at night. He dreamed, and wakened with a feeling of smothering. After sitting up for an hour or more, he could go back to sleep. He experienced no difficulty when walking on the level, but climbing two flights of stairs caused trouble.

The patient's *family history* revealed nothing of note. His *past history* was negative, except for a gonorrheal infection contracted when he was a boy. He had successfully passed a life insurance examination 31 years ago. His wife was living and in good health and had had no miscarriages; he had four children living, all of whom are healthy.

*Physical examination* revealed a small, thin man, in no apparent distress. His right pupil was slightly larger than the left. Reaction to light was sluggish. There were no palpable glands. His teeth were in bad condition. A rather marked pulsation in the vessels of the neck was noted. The apex beat was felt in the fifth and sixth intercostal space, well outside the mid-clavicular line. No thrills and no shocks were present. The heart rate, when standing, was 96, the rhythm regular. A short, systolic murmur could be heard at the base on each side of the sternum, followed by a blowing, diastolic murmur, loudest over the aortic area and transferred downward on each side; this murmur was especially noticeable in the fourth intercostal space, to the left, near the sternum. When the patient was lying down, a faint systolic murmur at the apex could also be heard. His pulse was of the Corrigan type. The arteries were thickened. The blood pressure in the left arm was 150/50 and in the right arm 140/60. Examination of the lungs revealed coarse râles over both sides of the chest; a few moist râles could be noted at the bases, posteriorly. Knee jerks were present. The abdomen showed nothing abnormal and there was no edema of the extremities. The Wassermann reaction was positive (++++). A faint trace of albumin was found in the urine. Fluoroscopic examination of the chest revealed enlargement of the left ventricle and some dilatation of the aorta.

The electrocardiogram made on the day the patient was first seen is shown in Fig. 1. The following day he began taking bichlorid of mercury,  $\frac{1}{4}$  grain and potassium iodid, 10 grains, 3 times daily.

The patient returned after 16 days of comparative inactivity feeling somewhat better. The electrocardiogram made at this time (Fig. 2) showed inversion of the *T* wave in Leads I and II and almost flat *T*-3. Medication with potassium iodid and mercury was discontinued on February 17.

On March 3, the patient reported having experienced one attack of dyspnea at night. Physical examination showed no change. In the electrocardiogram (Fig. 3) the *T* waves were upright in Leads II and III and diphasic in Lead I. Administration of bichlorid of mercury and potassium iodid was resumed in the same dosage.

The patient, when seen on March 10 was feeling about the same. In the electrocardiogram taken on this day (Fig. 4), the changes in the *T* waves in all leads can be noted. Dosage of potassium iodid was increased to 15 grains 3 times daily, continuing the bichlorid of mercury as before.

On March 17, the patient reported feeling much improved. The electrocardiogram of this date (Fig. 5) shows an increase in the inversion of the *T* wave in Leads I and II, approaching that of the coronary type. Administration of mercury and potassium iodid was discontinued.

On March 24, some dyspnea was reported. Fig. 6 of this plate shows the *T* wave upright in Leads II and III and diphasic in Lead I. The same dosage of bichlorid of mercury was resumed with 15 grains of potassium iodid 3 times a day.

The patient reported feeling much better on March 31. The physical examination showed no variance. Marked changes in the *T* waves in all leads are to be noted in Fig. 7. Medication was discontinued.

On April 7, he felt not quite so well, although the physical examination showed no change. The differences in the *T* waves at this time are shown in the electrocardiogram in Fig. 8. Potassium iodid (15 grains, 3 times daily) without mercury was prescribed.

On April 14, the patient reported one attack of dyspnea without definite change in the findings of physical examination. The variations in the *T* wave in all leads when he was taking potassium iodid without mercury are to be noted in Fig. 9. Potassium iodid was discontinued and administration of  $\frac{1}{4}$  grain of bichlorid of mercury, 3 times daily, was resumed.

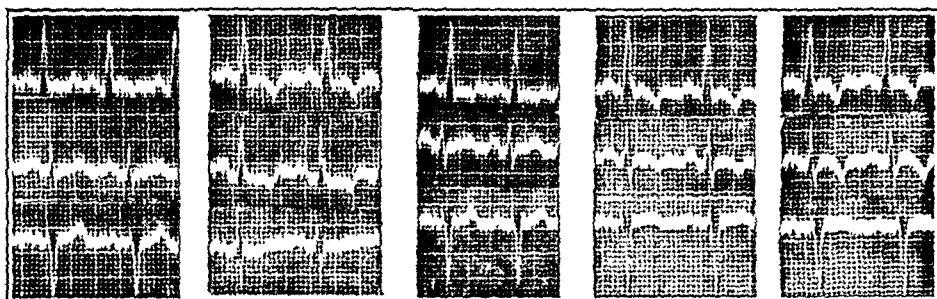


FIG. 1.  
2-1-34.

FIG. 2.  
2-17-34.

FIG. 3.  
3-3-34.

FIG. 4.  
3-10-34.

FIG. 5.  
3-17-34.

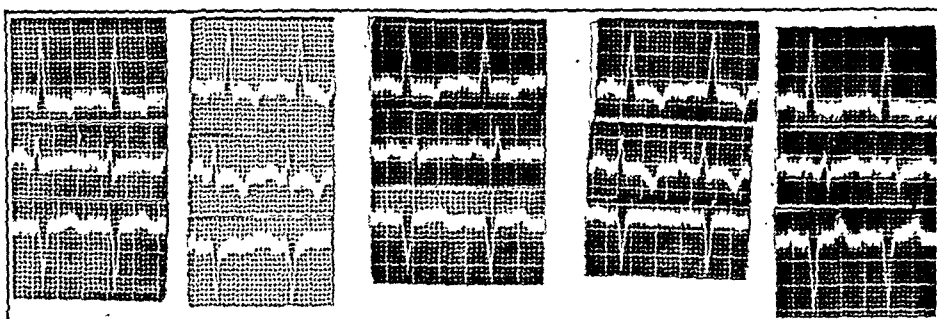


FIG. 6.  
3-24-34.

FIG. 7.  
3-31-34.

FIG. 8.  
4-7-34.

FIG. 9.  
4-14-34.

FIG. 10.  
4-21-34.





The patient reported increased shortness of breath on April 21. From the electrocardiogram (Fig. 10), it can be seen that the *T* waves had become upright in Leads II and III and were only slightly inverted in Lead I.

It would therefore seem that the potassium iodid was the cause of the variations in the *T* waves, since they occurred when he was taking potassium iodid without mercury and disappeared when he took mercury without potassium iodid. During the course of this study the patient remained at home in comparative inactivity. It is believed that the changes seen in these curves are brought about by the effect of the potassium iodid on the luetic lesion near the orifices of the coronary arteries. When the use of potassium iodid was discontinued the reaction subsided, the blood supply to the ventricles was reestablished and the marked changes in the *T* waves disappeared. Other minor changes in the form of the curves may be noted, but the *T* waves were the chief interest in this study.

The patient has not returned for further observation.

**Summary.** A case of luetic heart disease is presented, showing marked changes in the electrocardiogram, following the administration of potassium iodid, which disappeared when the potassium iodid was stopped, to recur when the iodid was renewed. It is believed that further study will cause a change in the prevalent ideas regarding the treatment of this condition, and that such a study may also be useful in diagnosis. No similar changes in other heart conditions have been noted, in the few cases observed.

## AURICULAR FIBRILLATION IN HYPERTHYROIDISM.

### THE INFLUENCE OF AGE.

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HYPERTHYROIDISM has long been recognized as one of the common causes of auricular fibrillation. In a recent study by one of us (Smith) hyperthyroidism ranked second as a cause of this cardiac arrhythmia. The exact incidence of auricular fibrillation in hyperthyroidism has varied considerably in different localities and in the clinical material studied by different investigators. The present study was undertaken to determine the influence of age in the production of auricular fibrillation among patients with hyperthyroidism. The clinical material providing the basis for the study consisted of cases in which operation was performed, of exophthalmic goiter and of hyperfunctioning adenomatous goiter. The aim was to take for study 100 cases of exophthalmic goiter, representing each of the first eight decades of life, or 800 cases in all, and a similar number, similarly distributed, of cases of hyperfunctioning

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adenomatous goiter. However, in some decades of life 100 cases were not available. Adenomatous tissue in the thyroid gland rarely produces hyperthyroidism before the age of 20; few patients with such a condition were in the second decade of life and none in the first. Although exophthalmic goiter is not so uncommon before the age 20, only a few patients were in the first decade of life. For various other reasons, the number of patients with exophthalmic goiter and the number with hyperfunctioning adenomatous goiter who were in the eighth decade of life fell short of 100.

**Classification.** The presence of auricular fibrillation in hyperthyroidism by no means precludes a return to normal sinus rhythm. In many cases a transient period of auricular fibrillation occurs during the immediate postoperative interval, and at no other time. Cases of this type comprise the larger part of the group we have classified as instances of intermittent auricular fibrillation. We have also included in this group those patients who had auricular fibrillation before as well as after operation, and whose cardiac rhythm returned to normal following thyroidectomy. The preoperative period of fibrillation of some of these patients was of fairly long standing; of others, it was limited to one or more paroxysmal attacks. Undoubtedly many patients with hyperthyroidism have short periods of auricular fibrillation which the clinician has no opportunity to observe.

Those patients with auricular fibrillation, whose arrhythmia was constantly present during the time the patient was under observation, we have classified as having continuous auricular fibrillation. The period of observation usually comprised several days to 3 weeks before operation, and 2 to 3 weeks after operation. Later observations make it certain that in some cases of prolonged auricular fibrillation, normal sinus rhythm is reestablished after a greater length of time. In other cases the auricles fibrillate indefinitely. The number of patients whose normal cardiac rhythm is reestablished after leaving the clinic cannot be accurately determined.

*Age.* Table 1 shows the incidence by decades of auricular fibrillation in exophthalmic goiter and in hyperfunctioning adenomatous goiter. It also shows the relative incidence, by decades, of the continuous and intermittent types of auricular fibrillation found in each type of hyperthyroidism, as well as the number of postoperative deaths of patients with auricular fibrillation.

Auricular fibrillation was absent before the age of 20, uncommon before the age of 40 and very frequent after the age of 50. Rising rapidly in the sixth decade, the incidence of auricular fibrillation continued to mount during the seventh decade and reached a maximum of about 50% in the eighth decade.

Table 2 shows the incidence by decades of auricular fibrillation in exophthalmic goiter and in hyperfunctioning adenomatous goiter after exclusion of certain complicating factors.

TABLE 1.—AGE INCIDENCE OF AURICULAR FIBRILLATION IN HYPERTHYROIDISM.

Decade of life.	Exophthalmic goiter.						Hyperfunctioning adenomatous goiter.					
	Cases.	Auricular fibrillation.					Cases.	Auricular fibrillation.				
		Cases.	Per cent.	Postoperative deaths.	Continuous fibrillation.	Intermittent fibrillation.		Cases.	Per cent.	Postoperative deaths.	Continuous fibrillation.	Intermittent fibrillation.
0-9 . . .	13	0	0	0	0	0	0	0	0	0	0	0
10-19 . . .	100	0	0	0	0	0	15	0	0	0	0	0
20-29 . . .	100	3	3	0	0	3	100	2	2	0	0	2
30-39 . . .	100	1	1	0	0	1	100	5	5	0	0	5
40-49 . . .	100	4	4	0	3	1	100	11	11	0	2	9
50-59 . . .	100	22	22	1	11	11	100	33	33	2	8	25
60-69 . . .	100	29	29	1	9	20	100	50	50	0	23	27
70-79 . . .	22	12	55	2	5	7	82	38	48	4	14	24

TABLE 2.—AGE INCIDENCE OF AURICULAR FIBRILLATION IN HYPERTHYROIDISM AFTER EXCLUSION OF POSSIBLE ASSOCIATED ETIOLOGIC FACTORS OF HYPERTENSION, ARTERIOSCLEROSIS, ENDOCARDITIS AND PERICARDITIS.

Decade of life.	Exophthalmic goiter.			Hyperfunctioning adenomatous goiter.		
	Auricular fibrillation.		Total.	Auricular fibrillation.		Total.
	Continuous.	Intermittent.		Continuous.	Intermittent.	
0-9 . . .	0	0	0	0	0	0
10-19 . . .	0	0	0	0	0	0
20-29 . . .	0	2	2	0	2	2
30-39 . . .	0	1	1	0	4	4
40-49 . . .	0	1	1	1	7	8
50-59 . . .	8	9	17	3	17	20
60-69 . . .	5	13	18	7	17	24
70-79 . . .	4 (18%)	5 (23%)	9 (41%)	7 (8%)	12 (15%)	19 (23%)

*Incidence of Auricular Fibrillation in Exophthalmic Goiter and in Hyperfunctioning Adenomatous Goiter.* Whether hyperthyroidism is on a basis of adenomatous or of exophthalmic goiter, the patient who is over 50 is likely to have auricular fibrillation. The influence of age on the incidence of auricular fibrillation is similar in the two types of hyperthyroidism, considered separately.

Auricular fibrillation occurred more frequently in association with hyperfunctioning adenomatous goiter than in association with exophthalmic goiter in almost every decade of life. The slightly higher incidence of 3% in association with exophthalmic goiter in the third decade, as compared with 2% in association with hyper-

functioning adenomatous goiter in the same age group, is too small to be considered significant. The apparently higher incidence of 55% in cases of exophthalmic goiter in the eighth decade, as compared with 48% in cases of hyperfunctioning adenomatous goiter, may be due to the small group of cases of exophthalmic goiter (22) which was available for study, as compared with the larger group of cases of hyperfunctioning adenomatous goiter (82).

*Incidence of Continuous and Intermittent Types of Auricular Fibrillation.* The cases in which auricular fibrillation was intermittent outnumbered those in which it was continuous, both among those of exophthalmic and among those of hyperfunctioning adenomatous goiter, and in younger as well as older age groups.

Advancing age determines an increase in frequency of occurrence of cases of intermittent and also of continuous auricular fibrillation.

No patient under 40 was found to have continuous auricular fibrillation. Among the handful of patients in the third and fourth decades of life arrhythmia was a temporary departure from the normal.

TABLE 3.—DURATION OF INTERMITTENT AURICULAR FIBRILLATION OCCURRING FOLLOWING THYROIDECTOMY.

Decade of life.	Exophthalmic goiter.				Hyperfunctioning adenomatous goiter.			
	Cases.	Duration of auricular fibrillation, days.			Cases.	Duration of auricular fibrillation, days.		
		Mini-mum.	Maxi-mum.	Aver-age.		Mini-mum.	Maxi-mum.	Aver-age.
0-9	0	0	0	0	0	0	0	0
10-19	0	0	0	0	0	0	0	0
20-29	3	1	3	2.0	2	1.0	4	2.5
30-39	1	4	4	4.0	5	1.5	4	3.1
40-49	1	3	3	3.0	9	1.0	8	3.4
50-59	11	1	8	3.5	25	1.0	41	4.6
60-69	20	1	6	2.2	27	1.0	14	3.8
70-79	7	1	11	4.0	24	1.0	25	4.1

*Duration of Auricular Fibrillation Following Thyroidectomy.* In many cases in which transient fibrillation of the auricles developed following thyroidectomy, the abnormal rhythm lasted only a few hours. In a few it persisted as long as 10 days. Accurate observations regarding the duration of the period of fibrillation had not been noted in the records of all cases. Table 3 shows the average duration of postoperative auricular fibrillation for the patients in each decade. The hearts of patients with hyperfunctioning adenomatous goiter usually required longer to reestablish a normal rhythm than did those of patients with exophthalmic goiter; this tendency was noticeable not only for the series as a whole, but in almost every decade.

*Cardiac Decompensation.* Cardiac decompensation of varying severity occurred in 25 of the 71 cases of exophthalmic goiter with auricular fibrillation; and in 37 of the 139 cases of hyperfunctioning adenomatous goiter with auricular fibrillation. Cardiac decompensation probably resulted in 33 of these 62 cases from a combination of hyperthyroidism and complicating disease of the heart. In 15 cases of exophthalmic goiter and in 14 of hyperfunctioning adenomatous goiter no cause for the cardiac decompensation other than hyperthyroidism could be found.

*Influence of Hypertension and Intrinsic Cardiac Disease.* Of 85 patients who had hyperthyroidism associated with hypertension, arteriosclerosis, endocarditis or pericarditis, 77 (91%) were over 50. Of 125 patients who had hyperthyroidism associated with none of these extraneous factors, 107 (86%) were over 50. In the case in which circulatory reserve has been reduced by previous organic heart disease, it is not surprising that the added burden of hyperthyroidism should result in myocardial insufficiency. That the increased incidence of auricular fibrillation, cardiac enlargement and decompensation among patients with hyperthyroidism who are over 50 is to be attributed wholly to the frequent occurrence of hypertension and coronary sclerosis at this period of life would appear to be incorrect. A large number of older patients with hyperthyroidism who had auricular fibrillation or other manifestations of cardiac injury gave no evidence of hypertension or of previous independent heart disease.

*Influence of Duration and Intensity of Hyperthyroidism.* Plummer has pointed out that although the onset of exophthalmic goiter is, as a rule, relatively acute, the onset of hyperthyroidism in adenomatous goiter is usually insidious; that in the former condition, patients come under observation on an average of 9 months after the onset of the goiter, whereas in the latter they come under observation on an average of 17 years after the appearance of the goiter, and on an average of 3 years after the onset of toxic symptoms. He wrote: "The latter complex (hyperfunctioning adenomatous goiter) may extend over months without attracting much attention; on the other hand, exophthalmic goiter brings the patient to the physician relatively early and with a syndrome readily interpreted."

Auricular fibrillation and cardiac decompensation resulting from hyperfunctioning adenomatous goiter may not be associated with any definite symptoms of hyperthyroidism. In such cases a considerable length of time often elapses before it is recognized that the goiter is the cause of the myocardial injury. The higher incidence of auricular fibrillation and of other signs of myocardial insufficiency in hyperfunctioning adenomatous goiter, as compared with exophthalmic goiter, is due chiefly to the different distribution by age in the two diseases (Table 4); 78% of patients with hyperfunctioning adenomatous goiter are over 40, whereas 61% of patients

with exophthalmic goiter are under 40. However, if patients in similar age groups are compared, there is a slightly higher incidence of auricular fibrillation in association with hyperfunctioning adenomatous goiter than in association with exophthalmic goiter. One cause for this may be the longer duration of hyperthyroidism in adenomatous goiter. Some writers are inclined to ascribe major importance to duration of hyperthyroidism as a factor in the production of myocardial injury. Anderson, in a recent study, concluded that the presence of auricular fibrillation among patients with hyperthyroidism seems to depend on two factors: (1) Duration of symptoms, and (2) severity of the condition. Andrus found that the average duration of symptoms was conspicuously greater among patients with myocardial insufficiency. Without a control series, analysis of the 210 cases of auricular fibrillation in our series does not permit definite conclusion in regard to the influence of duration and intensity of hyperthyroidism in the production of myocardial injury. However, our data indicate that age is a much more important factor than duration of symptoms or than intensity of hyperthyroidism.

TABLE 4.—INFLUENCE OF INTENSITY AND DURATION OF HYPERTHYROIDISM ON INCIDENCE OF AURICULAR FIBRILLATION.

Decade of life.	Exophthalmic goiter (cases with auricular fibrillation).			Hyperfunctioning adenomatous goiter (cases with auricular fibrillation).		
	Average basal metabolic rate	Average duration of hyperthyroidism, mos.	Percentage of cases of exophthalmic goiter in which auricular fibrillation occurred.	Average basal metabolic rate.	Average duration of hyperthyroidism, mos.	Percentage of cases of hyperfunctioning adenomatous goiter in which auricular fibrillation occurred.
0-9		...	0	...	...	0
10-19		...	0	...	...	0
20-29	+46	14	3	+51	14	2
30-39	+28	9	2	+25	26	4
40-49	+30	3	3	+41	21	11
50-59	+38	25	21	+30	28	33
60-69	+39	15	30	+31	31	50
70-79	+44	15	54	+34	38	48
Averages for entire group with auricular fibrillation	+39	14	...	+32	31	...

The average duration of symptoms and the average basal metabolic rates for the patients who had auricular fibrillation, cardiac enlargement and cardiac decompensation are given in Table 5.

TABLE 5.—DURATION OF SYMPTOMS AND METABOLIC RATES OF PATIENTS WITH VARIOUS CARDIAC CONDITIONS.

	Exophthalmic goiter.		Hyperfunctioning adenomatous goiter.	
	Duration of symptoms, mos.	Metabolic rates, %.	Duration of symptoms, mos.	Metabolic rates, %.
Intermittent auricular fibrillation	14.3	+39.5	31.1	+32.8
Continuous auricular fibrillation	16.6	+40.0	32.0	+33.5
Cardiac enlargement	15.8	+40.2	22.4	+33.8
Cardiac decompensation	19.3	+41.5	24.6	+38.6

The fact that for comparable age groups there is a higher incidence of auricular fibrillation in association with hyperfunctioning adenomatous goiter than in association with exophthalmic goiter indicates, when considered in conjunction with the lower basal metabolic rates which obtain in adenomatous goiter, that intensity of hyperthyroidism is not a very important factor in producing the arrhythmia. The duration of the period of auricular fibrillation and the chance of the arrhythmia being replaced by normal sinus rhythm are probably not greatly influenced by the basal metabolic rate.

**Conclusions.** Subjected to the effects of hyperthyroidism, old patients are prone to have auricular fibrillation; young patients, to maintain normal cardiac rhythm. The increased incidence of auricular fibrillation among older patients with hyperthyroidism is only partially attributable to the frequent occurrence of coronary sclerosis and hypertension after the age of 40. Advanced age itself, although unaccompanied by these processes, determines an increased susceptibility of the heart to auricular fibrillation and adds to the likelihood of its becoming decompensated under the stress of hyperthyroidism.

Among 210 cases of auricular fibrillation associated with hyperthyroidism, cardiac enlargement occurred in 79, in 35 of which there was no evidence of hypertension or of preëxisting cardiac disease. In the same group of cases of auricular fibrillation, cardiac decompensation was present in 62; in 29 of these, hyperthyroidism was the only cause found for the cardiac decompensation. In only 2 cases did cardiac enlargement or decompensation afflict patients under 40.

Auricular fibrillation resulting from hyperthyroidism is more often transient or intermittent than prolonged or continuous, especially when not accompanied by serious myocardial injury. The arrhythmia often develops, for the first time, during the immediate postoperative period, in which case it ceases spontaneously within a few hours to a few days. Even when cardiac injury has occurred, the fibrillation of the auricles is frequently



replaced by normal sinus rhythm, when the heart has been relieved of the strain of hyperthyroidism.

Hyperfunctioning adenomatous goiter results in auricular fibrillation and other signs of myocardial insufficiency more often than does exophthalmic goiter. This different incidence in the two types of goiter results mainly because patients with adenomatous goiter acquire hyperthyroidism on an average of about a decade later in life than do those with exophthalmic goiter. The longer duration of hyperthyroidism in adenomatous goiter is a less important factor in producing the higher incidence of myocardial injury in this disease. Advanced age seems a much more important factor than duration or intensity of symptoms in determining the incidence of auricular fibrillation and myocardial insufficiency of patients with hyperthyroidism.

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### OBSERVATIONS ON PROGNOSIS IN ANGINA PECTORIS.

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STUDIES dealing with prognosis in angina pectoris are not lacking. The present report, which will be presented without reference to existing literature, is deemed of interest because it comes from a cardiac clinic in which arteriosclerotic heart disease is the predominant type. The average age of patients for whom a diagnosis of organic cardiovascular disease is made is 58 years. Approximately one-sixth of these patients include among their symptoms pain, either effort pain or pain related to coronary thrombosis. This study is based on the records of 166 patients who complained of effort angina. The term angina pectoris is used as Heberden described it and care has been taken to exclude those in whom effort pain first appeared after coronary thrombosis. It is hardly

necessary to state that there are undoubtedly errors in diagnosis and in the given causes of death. It is also recognized that the series itself is too small for mathematical treatment. Because of this fact and the unavoidable errors inherent in any such clinical study it is emphasized that the various figures given can have at best qualitative and never quantitative values.

Of these 166 patients, only 23 (about 14%) were women. The relatively low incidence of true angina in women is well known, but this small figure is the more striking because women constitute about 56% of the patients of this institution, and men, 44%. Of those suffering from cardiovascular disease, however, men predominate and the figures just given are reversed. The clientele of the institution does not represent a true cross-section of society, and any classification of this group on the basis of occupation would not be of significance for the social distribution of the disorder under consideration, but such classification does, however, confirm certain current impressions. The largest single group, 71 cases, comprised business men and executives. The second largest group was that of the physicians, 18 patients. The mechanics and farmers, of whom there were 15, outnumbered the groups of lawyers, of clergymen and of teachers.

In this presentation emphasis will be laid on the age at onset, age at death and duration of symptoms. The mean age at which pain first appeared was 57.5 years. The mean age at death was 63.3 years. Of greater interest than these averages is the distribution according to age groups, which is shown in Chart I. It will be seen that 65% did not develop pain until after 55. Of the entire group, 70% lived for 60 or more years. One patient, aged 47, had suffered from angina for only 4 months when he died from coronary thrombosis; the other extreme was a man who had angina for 24 years and died at the age of 82. The average duration of life for the whole series was 5.8 years; for those whose angina began between the ages of 45 and 74, the average was 6 years. The duration of life related to the age at onset is shown in Table 1, and in the bottom line of this table will be found the number of cases for each duration period. Fifty-four patients (32.5%) lived for 3 years or less. More detailed examination of this 3-year group is desirable and will help to explain the short duration of life of these people. Eighteen of these cases developed angina between the ages of 60 and 64, while 11 did not acquire the symptom until they had passed 65 years. Nineteen, or 36% of the 3-year group, suffered from essential hypertension, and 8 had hypertension of the arteriosclerotic type. There were serious complicating diseases in 6 patients, and also in this group were encountered 6 instances of excessive use of tobacco and alcohol. Those who died from disease other than cardiovascular, and those who suffered from essential hypertension, and those who did not develop angina until after 65 years accounted

for 64% of the 3-year group. There were apparently but 8 cases, 15% of the 3-year group and 4.8% of the entire series, who died from uncomplicated arteriosclerotic heart disease before 60 years of age. If this 3-year group be set aside there remain 112 cases, with an average duration of life of 7.7 years. In any consideration of prognosis there are two factors which must never be overlooked. The first concerns longevity itself, and of this it may be said that there is at present no reason to believe that the three score years and ten

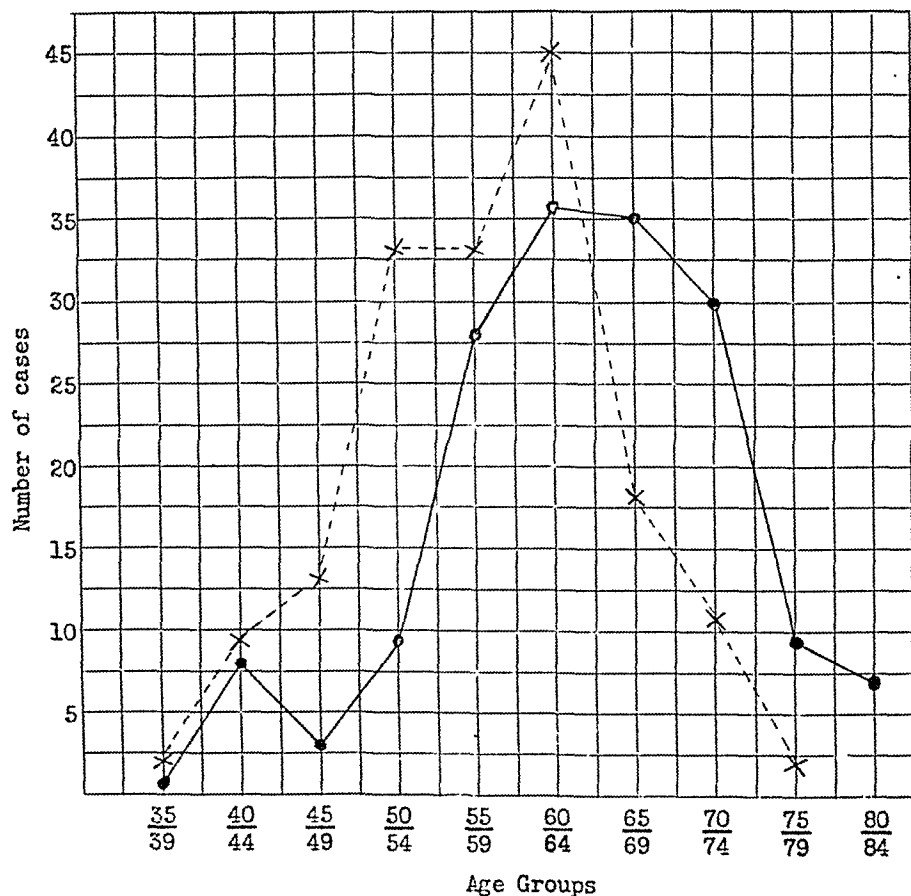


CHART I.—The distribution of 166 cases of angina pectoris according to age groups. Broken lines, age at onset; solid line, age at death.

allotted to man by the Psalmist will be extended. The available evidence rather indicates that the possible span of life by reduction on the final decades is shortening and not lengthening. The second factor is that of life expectancy, which at birth is now approximately 60 years, and is the greatest in recorded history. In this series, 30% of the patients died before 60; 70% reached or exceeded the present life expectancy, while 48% passed it by 5 or more years. It cannot be denied that the morbid process which underlies the

anginal syndrome does shorten life, and for the group of 112 patients, who began to suffer from angina at an average age of 57 years, there was a material reduction in the life expectancy estimated for that age. These people ought to have lived to an average age of 73.6 years. But by living to an average of 64.3 years they did complete 87% of the average lifetime of all persons who survive to the age of 57. One certainly would not attempt to minimize the seriousness of angina pectoris for the individual victim, but there is apparent in this disorder a striking disparity between the particular and the general. For the afflicted person the syndrome often constitutes a painful, even terrifying disease; it may cause serious limitation of activity, and for the individual the only thing

TABLE 1.—DURATION RELATED TO AGE AT ONSET.

Age at onset, yrs.	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	17	19	24	No. of cases.	Av. for group.
35-39	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	2	3.5
40-44	1	2	..	2	1	..	3	..	..	..	..	..	..	..	..	..	..	..	9	3.5
45-49	..	2	1	..	..	2	3	1	1	..	1	..	2	..	..	1	..	..	14	7.0
50-54	1	1	1	3	1	5	6	3	2	3	1	3	..	..	..	1	..	..	31	6.5
55-59	..	2	1	4	3	5	3	5	1	3	1	2	2	..	1	..	..	1	34	6.9
60-64	1	4	8	7	3	3	6	2	3	..	1	1	3	..	..	..	1	..	43	5.1
65-69	..	3	3	..	4	2	1	2	2	..	1	..	1	..	1	..	..	..	20	5.3
70-74	..	..	1	3	1	1	..	..	3	1	..	..	..	1	..	..	..	..	11	6.0
75-79	..	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	2.0
No. of cases	3	15	15	21	14	18	22	13	12	7	5	6	8	1	2	2	1	1	166	5.8

certain about his prognosis is its uncertainty. But in its general aspect, when the anginal syndrome is viewed, not as it presents itself in an individual, but in a large group, and in the light of average duration of symptoms, age at onset and age at death, and is compared with life expectancy and possible length of life, then angina pectoris seems much less grave and it does not stand out as a serious complication of arteriosclerotic heart disease.

The influence on prognosis of variation from normal is difficult to estimate, but the fact that 50% of these patients had, as far as is known, normal blood pressure levels throughout their course suggests that hypertension is not a factor of primary importance. There were 36 examples of typical essential hypertension, and of

these, 53% lived for 3 years or less after the onset of angina; in this group essential hypertension represented the primary disease in which angina appeared as a late complication. Scattered cases occurred after the 3-year period, but it is by no means certain that in these patients hypertonus was continuous. There were 45 patients who had transient periods of hypertension, or hypertension of the arteriosclerotic type, with high pulse pressure. For a number of patients this type of hypertension did not appear until angina had been present for several years. This latter type of hypertension reached its maximum incidence in the 5-year duration period, after which it was less frequently encountered. It is of interest to note that 68% of the women had hypertension compared to 50% of the entire group, and that the average age at death for the women was 67.1 years, nearly 4 years beyond that of the group as a whole.

The simultaneous existence of complicating factors occurred in less than one-fifth of these patients. Even when these were such as to suggest some causal relation, it was not possible to evaluate their rôle in prognosis. There were 9 instances of diabetes mellitus. Malignancy, gastro-intestinal and pulmonary disease occurred infrequently. The low incidence of prostatism was rather striking. There were but 3 known cases of rheumatic heart disease and 3 cases of luetic infection. Excessive use of tobacco was noted 16 times; 6 of these patients were in the group that lived for 3 years or less. On the other hand, the patient who had angina for 24 years used tobacco liberally, and another who used tobacco to excess also had diabetes for 6 years and had borne his angina for 3 years, when he died from coronary thrombosis, but at the age of 76 years. However, one may question whether the low incidence of excessive use of tobacco in the entire group, less than 10%, and the unusually long duration of life with angina in the series are in any way related. Examples of obesity occurred in all groups and that state appears to have no bearing on prognosis. Seventeen patients had 19 surgical operations, 8 tonsillectomies and 11 major operations. There were 2 operative deaths, but whether or not these were of cardiac origin, cannot be stated. In general, it does not appear that angina pectoris by itself constitutes an undue risk if surgical intervention is indicated. Unfortunately, this study can throw no light on the effect on prognosis of adequate medical control of patients who have angina. A few examples suggest that the submission to supervision might in many instances prolong life. The most striking case in this series presented at the age of 51 years, in addition to effort angina of 2 years' standing, obesity, hypertonus, pulsus alternans, congestive failure, cardiac enlargement and an abnormal electrocardiogram, and yet this man lived for 9 years, when he died from coronary thrombosis. It is known that he lived very carefully during those years. Another man, a severe diabetic with angina, lived for 6 years during which he violated for much of the time all

the rules laid down for diabetes and heart disease; it seemed as though with reasonable care this patient might have gone on much longer. On the other hand, the case of shortest duration who died at 47 years had extensive coronary artery disease which was not even suspected until a few months before death and certainly could not have been influenced by any now known measures. From the study of this particular series the impression is gained that examples similar to the last cited are relatively uncommon and that co-operation of the patient with reasonable medical control is worthy of trial.

There were electrocardiograms for most patients and for a few interesting serial records. While at times helpful for diagnosis, it is quite certain that the standard lead electrocardiogram is of no value for prognosis. Inversion of  $T$  in Lead I seemed to be the abnormality most frequently associated with effort angina. As the cardiac lesion progressed inversion of  $T_2$  appeared. There were numerous cases with a definite history of pain for 3 to 5 years before any abnormalities were recorded, and in one instance the electrocardiogram was still normal 13 years after the onset of angina. One patient had a normal electrocardiogram 3 days, and another 5 days before death from coronary thrombosis. In 3 cases there was  $T$ -wave inversion before the onset of angina. One patient had left axis deviation and deep inversion of  $T$  in the first lead 9 years before death occurred. Disturbances of rhythm other than premature beats were rare. There was one example of transient auricular fibrillation, one of permanent fibrillation (with mitral stenosis) and one of auricular flutter, which probably followed coronary thrombosis.

This series does not contain sufficient data for a satisfactory evaluation of the influence of heredity. The mean age at death of the patients was 63.3 years. For those known, the mean age at death of the fathers was 65.4 years, and for the mothers, 68.9. These are uncorrected figures and include such factors as early deaths of mothers from childbirth, and early death of either parent from acute infection or accidents. Cardiovascular disease was the cause of death for 37.5% of fathers, at a mean age of 64.5 years, and for 28.4% of mothers, at a mean age of 68 years. More mothers died from senility than from cardiovascular disease. There were several examples of patients who exceeded the span of their parents, who were likewise victims of cardiovascular disease. One does encounter families with a remarkable incidence of arteriosclerotic heart disease which may well be attributed to transmission from one parent, but such family histories are comparatively infrequent in this clinic. For this particular series of cases, when one considers the low familial incidence of cardiovascular disease and that duration of life of both patients and parents has exceeded their life expectancy at birth, heredity apparently is not an important

factor in prognosis, and from this study it is difficult to see how inherited defects in the vascular system can play a very large part in the present high incidence of arteriosclerotic heart disease.

Study of the causes of death in this series points to the high probability that a patient who has effort angina will die a cardiac death. For 15 patients nothing is known concerning the manner of death. Fifty patients died suddenly; the mechanism is not known in 16 of these. There were 87 deaths attributed to coronary thrombosis and 21 deaths from congestive heart failure; some of the latter may have been preceded by that accident, but this is not known. Thirteen deaths were ascribed to cerebral accidents. Thus, over 80% of the entire series died from cardiac or vascular disease. For the remainder the causes of death were variable and need not be enumerated; there were 3 suicides; other causes did not include more than 2 cases in any one group.

**Summary.** A study was made of 166 cases of effort angina, seen in a clinic in which arteriosclerotic heart disease is the predominant type. The influence of hypertension, obesity, familial vascular disease and certain miscellaneous factors has been considered. Electrocardiograms were available for most patients, but were found of no value for prognosis. Nearly one-third of these patients died suddenly, and over half died from coronary occlusion. Cardiac or vascular disease was responsible for death in over 80% of the series. The average duration of life in this series, 5.8 years, was greater than is usually anticipated. While prognosis in the individual case must always be uncertain, when viewed in the light of its comparatively long duration, and the late ages at onset and death, compared with life expectancy, the anginal syndrome appears less grave and does not stand out as a serious complication of arteriosclerotic heart disease, with which it is most commonly associated.

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## THE EFFECT OF BACTERIA ON THE NORMAL STOMACH AND ON ACUTE EXPERIMENTAL GASTRIC ULCER IN DOGS.\*

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IN a previous experimental study<sup>1</sup> on the production of gastric ulcer it was found that the gastric tissue showed a resistance to

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acids up to a certain strength. It was determined, for example, that ulcers could be produced in most instances by the injection of a 1% hydrochloric acid solution into the gastric tissue while the injection of lesser strengths of this acid produced inconstant results. These ulcers have a tendency to heal rapidly, usually within a period of 3 weeks. Chronic ulcers could not be produced by this method alone.

A review of the literature on this subject reveals many different opinions regarding the effect of bacteria in the production of chronicity of gastric ulceration. Since it has been maintained by many who have investigated this problem that chronic ulceration is due to, or augmented by, a secondary infection, we thought it advisable to bring the gastric mucosa and the acute ulcer into intimate contact with potent cultures of the common organisms.

Dogs were used in our experiments because we could easily produce acute ulcerations without disturbing the mucosa from within and without resorting to any major operative procedures. It is agreed by most observers that acute ulcers in healthy animals heal rapidly no matter how produced.

*The Effect of Gastric Secretion Upon Bacteria.* According to Bartle and Harkins,<sup>2</sup> gastric contents are by no means sterile. They have found that practically no germicidal value could be demonstrated at concentrations of free hydrochloric acid below 0.04%; but gastric juice containing from 0.08% upward had a well-marked bactericidal effect. Johnson and Arnold<sup>3</sup> found that the free acid gastric contents of dogs did not kill bacteria but exercised only a bacteriostatic influence on the flora. Knott,<sup>4</sup> on the other hand, has shown that free hydrochloric acid in a strength less than that found in the average normal stomach is sufficient to destroy many forms of bacteria, especially streptococci.

Van der Reis<sup>5</sup> dipped little cubes of bacon and apple seeds, to which threads were tied, into prodigious and staphylococcus cultures and had the patient swallow them. From these the bacteria could be cultivated when they were withdrawn 1 or 2 hours later.

Bartle reports that gastric juices from 10 to 20 degrees free hydrochloric acid were more germicidal for *Streptococcus viridans* and *B. coli communis* than for *Staphylococcus aureus*; the latter organism even in higher degrees of acidity showed considerable resistance.

Interestingly enough, Andrews and his coworkers<sup>6</sup> have demonstrated that bacteria already present locally in tissue can be made to multiply when the area is damaged in certain ways.

In our experiments we thought it best to administer the bacteria mixed with food in order (1) to dilute and neutralize the gastric contents, and (2) so that the bacteria would not only remain in the stomach for longer periods but would be protected from "acid" attack by their admixture with the food. We also administered



bacteria alone in one group of animals, and in another group we gave large amounts of sodium bicarbonate in order to neutralize the gastric acidity at the same time that the bacteria were in the stomach.

In another series of experiments we produced ulcerations in the stomach, by injection of hydrochloric acid into the gastric wall and fed the animals with bacteria alone and bacteria with the addition of sodium bicarbonate. The bacteria were of the following potency: *Streptococcus*, 1.5 billion per cc.; *B. coli* and *staphylococcus*, 5 billion per cc. The site of the injection had been marked with a bead.

The preliminary group of experiments are briefly recorded in Table 1.

TABLE 1.—EXPERIMENTS WITH NORMAL GASTRIC MUCOSA.

No. of dogs.	Time, days.	0.5 cc. culture injected into stomach wall (24-hr. broth).	Site of injection.	10 cc. bacteria fed daily.	NaHCO <sub>3</sub> fed daily.	Mucosa at autopsy.	Remarks.
2	18	<i>Staph. aureus</i>	Lesser curva.	None	None	Normal	Control.
2	20	<i>Staph. aureus</i>	Lesser curva.	<i>Staph. aureus</i>	None	Normal.	
2	6	<i>Staph. aureus</i>	Lesser curva.	<i>Staph. aureus</i>	1 ounce	Normal.	
2	20	<i>Staph. aureus</i>	Lesser curva.	<i>Staph. aureus</i>	1 ounce	Normal.	
2	30	<i>S. viridans</i>	Lesser curva.	None	None	Normal.	
2	28	<i>S. viridans</i>	Lesser curva.	<i>S. viridans</i>	None	Normal.	
2	28	<i>S. viridans</i>	Lesser curva.	<i>S. viridans</i>	1 ounce	Normal.	
1	30	None	None	<i>S. viridans</i>	None	Normal.	
2	37	<i>B. coli</i>	Lesser curva.	None	None	Normal.	
1	25	<i>B. coli</i>	Lesser curva.	<i>B. coli</i>	None	Normal.	
2	25	<i>B. coli</i>	Lesser curva.	<i>B. coli</i>	1 ounce	Normal.	

It is interesting to note that Best and Orator<sup>7</sup> injected into the stomach wall of rabbits 2 cc. of a  $\frac{1}{100}$  *Staphylococcus aureus* (24-hour) culture. All of their animals died within 48 hours and yet the pathologic picture at autopsy was quite innocent.

Our work recorded in Table 1 on *S. viridans* is confirmed by Türk,<sup>8</sup> who injected streptococci into the mucosa of the stomach with negative results. He also fed large amounts of streptococci (and *B. coli communis*, separately) which were given daily at a time when the stomach was empty to dogs in which an experimental abrasion was made in the pyloric and duodenal mucosæ with negative results. These findings were also confirmed by Wilensky and Geist.<sup>9</sup>

Saunders, Holsinger and Cooper<sup>10</sup> infected threads with a streptococcus isolated from resected peptic ulcers and inserted them into the wall of the stomach and duodenum, the thread passing through all three layers. Sections failed to show tissue changes microscopically. Our observations are in accord with the latter findings.

*The Production of Gastric Ulceration by Hydrochloric Acid.* In a previous communication<sup>1</sup> it had been shown that a 1% solution of hydrochloric acid produced an acute ulcer very constantly. These ulcers healed completely within a period of 7 to 21 days. In the

present experiments it was believed that the acute ulcers could be infected and in that manner become chronic. Ulcers were produced by the injection of 1% hydrochloric acid. Feedings with different bacteria, such as *Staph. aureus*, *B. coli* and *S. viridans*, potent enough to produce secondary infection of the ulcer, was instituted. The following experiments were carried out after the acute gastric ulceration had fully developed (Table 2).

TABLE 2.—EXPERIMENTS WITH MUCOSA WITH ACUTE GASTRIC ULCER PRODUCED BY HYDROCHLORIC ACID.

No. of dogs.	Time, days.	10 cc. bacteria fed daily.	NaHCO <sub>3</sub> fed daily.	Autopsy findings.	Remarks.
1	25	<i>Staph. aureus</i>	None	Definitely healed ulcer	Rugæ converged toward ulcer.
2	49	<i>Staph. aureus</i>	None	Definitely healed ulcer	Rugæ converged toward ulcer.
1	8	<i>Staph. aureus</i>	1 ounce	Deep ulcer	Elevated round edges—characteristic of indurated ulcer.
1	9	<i>Staph. aureus</i>	1 ounce	Perforating ulcer	Characteristics of acute ulcer.
2	19	<i>Staph. aureus</i>	1 ounce	Definite ulcer.	
1	49	<i>Staph. aureus</i>	1 ounce	Completely healed ulcer.	
2	21	<i>S. viridans</i>	None	No ulcer.	
2	21	<i>S. viridans</i>	1 ounce	Definite healing ulcers.	
1	35	<i>B. coli</i>	None	Definite healed ulcer.	
2	44	<i>B. coli</i>	None	Healed ulcer in 1; normal mucosa in other.	
1	3	<i>B. coli</i>	1 ounce	Perforated ulcer.	
1	12	<i>B. coli</i>	1 ounce	Perforated ulcer.	
1	15	<i>B. coli</i>	1 ounce	Small ulcer.	
1	27	<i>B. coli</i>	1 ounce	No ulcer.	

As a separate study the following experiments were performed: 0.5 cc. of 1% hydrochloric acid was injected through the serosa into the muscular walls of the stomachs of 3 dogs. Three days later, after the production of necrotic ulcers, 1 cc. of *S. viridans* (24-hour broth culture) was injected in each dog through the serosa into the muscular and submucosal areas surrounding the ulcers. In 1 of these dogs a healed ulcer was found after 34 days; in another, sacrificed 54 days after production of the ulcer, examination of the stomach showed an old healing perforated ulceration with the rugæ converging toward the ulcer, the base of which measured 2 mm. The third dog was sacrificed 57 days after ulcer production and no sign of ulceration could be discovered.

The same study was repeated except that gastrotomies were performed in order to visualize the ulcers and, therefore, to allow direct injections of bacteria into their walls from the mucosal side of the stomach. Four dogs had ulcers produced by injection of 1% hydrochloric acid. Three days later gastrotomies showed

definite ulcerations in each instance; 1 was actually perforated but was sealed off by omentum. The immediate area surrounding each ulcer was inoculated directly through the mucosa with 1 cc. of a 24-hour culture of *S. viridans*. The gastrostomy was closed in each instance. Two dogs were examined 59 days after ulcer production and both showed complete healing. There was some induration of the gastric wall in both cases (1 of these had perforated). In the other 2 animals the ulcers were also healed, but in 1 the gastric wall was perfectly normal; in the other there was only the slightest induration.

**Soda Controls.** In 2 dogs in which ulcers were produced by the injection of 1% hydrochloric acid, soda alone was given by mouth for 88 days. They were sacrificed and both revealed definite healed ulcers. In 2 other dogs in which soda was fed without the production of the acid ulcer, 1, after 19 days, revealed no gastric changes and in the other, after 88 days, the mucosa was normal.

Microscopic studies made of the gastric tissue surrounding the areas of injection of colon, streptococcus and staphylococcus bacteria revealed the following data: The mucosa was essentially normal; the submucosa in most instances revealed a slight edema and round-cell infiltration. In 1 instance a thrombotic vessel and in another a submucosal infarct were found. The muscularis was normal in most instances, but in 1 an area of necrosis and in another a slight infiltration of round cells were found. The serosa, in a few instances, showed evidences of localized peritonitis, and in 1 instance there were many small localized abscesses (staphylococcus). Although there were slight microscopic changes, the macroscopic appearances were entirely normal.

Test meals were made in a number of the dogs but the results obtained were not significant. The gastric contents were cultured in 5 instances with negative results. Blood cultures were made in 3 instances with negative results. In a few of the dogs fed with soda, CO<sub>2</sub>-combining power determinations of the blood were made and these also proved to be normal. Blood counts were normal in the 8 animals in which they were done.

**Summary.** Gastric ulceration has been regarded as due to a bacterial invasion of the gastric mucosa, the chronicity of ulcers being maintained by the infection. Other observers have stated that the chronicity of ulcers is dependent upon the effect of hydrochloric acid irritation. The consensus of opinion is that both factors are important in the chronicity of gastric ulceration and, since hydrochloric acid of normal strength fed to dogs does not produce a chronic ulcer, it would follow that if this view is correct the factor of bacterial infection might be of paramount importance.

The present experimental study deals with the effect of bacteria upon the normal gastric mucosa and upon the mucosa with acute gastric ulceration produced by hydrochloric acid. It was found that large amounts of bacteria mixed with food did not produce

ulceration nor mucosal irritation when fed to dogs. When bacteria were fed to dogs in which acute gastric ulceration had been produced by hydrochloric acid, no infection of the ulcer took place and chronicity was not noted, the ulcer healing completely, though in some cases in slightly prolonged time. Even after giving large amounts of sodium bicarbonate, the bacteria had no permanent effect upon the gastric mucosa or the acute ulcers.

After potent cultures of bacteria are injected into the gastric wall, infection with consequent abscess formation and necrosis does not generally take place in the dog's stomach.

In several instances gastrotomies, permitting direct inoculation of the ulcer walls with *S. viridans*, did not prevent rapid and complete healing of what were observed to be deep necrotic (in 1 instance, a perforated) ulcers.

The acute hydrochloric acid ulcer is a clean-cut, non-infected, necrotic ulcer which apparently does not lend itself to bacterial infection.

Chronic gastric ulceration cannot be produced by bacteria alone or by bacteria acting on acute hydrochloric acid ulcers, at least in the dog. It seems that another factor must play an important rôle in its chronicity.

The high acidity of the dog's gastric contents seems to inhibit the growth of bacteria; but this hardly explains the results obtained after neutralizing the gastric contents with food and alkalies given simultaneously with the bacteria.

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**BLOOD GLUCOSE CLEARANCE.****ITS DETERMINATION BY A MICROINTERVAL METHOD.****I. STUDIES IN NORMAL AND DIABETIC PERSONS.\*†**

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SINCE 1913 a vast literature has accumulated on the use of glucose tolerance tests as diagnostic and prognostic aids in diabetes mellitus, various endocrinal and nervous diseases, arthritis, carcinoma and many other diseases. Classified according to the route of administration of the glucose, these tests have been of two main types: the oral and the intravenous. The literature on the oral glucose tolerance test has been reviewed recently.<sup>1</sup> The inconsistencies of the test have been reëmphasized and explained by irregularities in gastric emptying. Work demonstrating marked variations in gastric evacuation in normal individuals and corresponding changes in the blood sugar curves has been cited.

To eliminate errors arising from differences in absorption, intravenous glucose tolerance tests have been devised. One of the earliest and still the most accurate of these was introduced by Woodyatt, Sansum and Wilder,<sup>2</sup> but the expense of the apparatus used and the length of time required for the test have made it impractical for routine use.

Other intravenous glucose tolerance tests have been carried out according to the following general plan: A quantity of glucose greater than the body can immediately dispose of is injected intravenously in a short period of time. Blood specimens are taken at fixed intervals thereafter and the tolerance is determined by the height to which the blood sugar rises and the time required for it to return to normal.

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The 23 tests of this type which we have found in the literature since 1913<sup>3</sup> differ widely in technical details but in our opinion have certain faults in common.

1. *Dosage.* In 17 of these tests, identical amounts of glucose were given to different patients regardless of body weight. In 1 of these, for instance (Jorgenson and Plum), the routine dose of 20 gm., when calculated in terms of body weight, gives amounts varying from 0.18 to 0.66 gm. per kg. These authors contended that the weight factor was unimportant. Yet in our experience, varying the dosage from 0.1 to 0.33 gm. per kg. results in corresponding changes in the height and duration of the curves, as illustrated in Chart 2.

2. *Injection Time.* In 7 of these tests the time allotted to the administration of glucose was not uniform; in 4 others it was not mentioned. We have found pronounced differences in duplicate curves when the injection time was increased from  $\frac{1}{2}$  to  $1\frac{1}{2}$  minutes with an otherwise constant technique and, therefore, feel that it is a factor warranting standardization.

3. *Number of Blood Specimens and Intervals of Collection.* In 22 of the 23 intravenous tests, collection of blood samples covered a period of 1 to 4 hours and necessitated several venous or capillary punctures. The discomfort incident to multiple punctures and the time consumed in carrying out these tests are serious drawbacks from the standpoint of both patient and laboratory.

**The Microinterval Technique.** *General Remarks.* In the modification to be offered in this presentation, an effort has been made to eliminate the undesirable features of other intravenous tests. For reasons stated above, the dosage of glucose was based on body weight.\* A dose of 0.2 gm. per kg. was chosen because it produced a curve whose blood sugar range closely approximated that obtained by the more familiar oral technique.

For comparable results, a uniform injection time is obligatory, and a period of  $1\frac{1}{2}$  minutes was chosen because it was most convenient for the quantities given.

Since a complete "arm to arm" circuit of the blood is made every 20 to 30 seconds,<sup>4</sup> it seemed reasonable to expect a distinctive response in normals and diabetics within a very few minutes after the injection of glucose. Klein and Holzer,<sup>3</sup> taking specimens at 30-second intervals, found definite differences in the curves of normals and diabetics within 6 minutes. Since their method involves puncture of the radial artery, it is not practical as a clinical test.

\* A tendency toward "diabetic curves" was found in obese subjects showing no clinical evidence of diabetes mellitus. It is probable that in this type of individual it would have been more accurate to have based the dosage on surface area rather than body weight, since the mass of active protoplasm is more nearly proportionate to the former.

By the use of a three-way stopcock between needle and syringe, it was possible to collect venous specimens at any desired time during a period of 15 minutes with but one insertion of the needle. At first specimens were taken 1, 2, 3, 4, 5, 6, 7, 10, 15 and 30 minutes after the completion of the glucose injection. The 1- and 2-minute readings were generally on the ascending limb of the curve, were not particularly informative and, therefore, were discarded. The *peak point* (highest reading) occurred between the 3d and 5th minute after the end of the injection and was clearly shown in samples collected every 60 seconds during this period. (Fifteen-second intervals were tried in a few cases but greatly increased the technical work and were of no apparent additional diagnostic value.) The descending limb of the curve was adequately shown by specimens at 5, 10 and 15 minutes. Although the blood sugar at the latter time was still above fasting level, little additional information was gained by prolonging the test to 30 minutes, since this phase of the curve was relatively asymptotic.

*Procedure.* At the risk of making the mechanics of the test seem cumbersome, the technique which we have used is described in detail.

The following material is needed: One 50-cc. syringe, graduated in units of 1 cc.; 2 three-way metal stopcocks; 2 18- or 19-gauge intravenous needles; 1 ampule of 50% glucose;\* 4 to 6 5- or 10-cc. syringes; oxalated test tubes; watch with second hand.

The patient, previously on a mixed diet, is directed to eat nothing after 6 o'clock on the evening before and to report at the laboratory between 8 and 9 o'clock the following morning. Fifty per cent glucose is drawn up into the large syringe to the amount of 0.2 gm. per kg. body weight, the three-way stopcock and needle attached and a vein in the antecubital fossa is entered with the valve so set that the blood flows through the side arm into an oxalated tube. After the fasting specimen has been collected, the tourniquet is released, the valve turned so that the needle and syringe are connected and the injection is started. While the injection is in progress, an assistant calls off 15-second intervals by the watch. One-sixth of the total amount of glucose is given during each 15-second period and the injection is finished in exactly  $1\frac{1}{2}$  minutes. Within the next  $2\frac{1}{2}$  minutes a tourniquet is applied to the opposite arm, a small syringe and three-way stopcock fitted to the other needle and a vein entered. The tourniquet is then removed and discarded and the needle is left *in situ* for the remainder of the test. Two- to 4-cc. blood samples are collected exactly 3, 4, 5, 10 and 15 minutes after the end of the injection.

After each specimen has been collected, the valve is turned so that syringe and side arm are connected, the syringe detached and replaced by a clean dry one. With each change of syringe, air is forced through the stopcock so that residual blood is ejected through the side arm. In the intervals between the last 3 specimens, the valve is so set that the needle and syringe are connected and sufficient suction is applied to remove 1 or 2 cc. of blood per minute. This is merely an additional precaution to prevent clotting and the blood so obtained is discarded.

\* Commercial ampules of 50% glucose were used, largely for the sake of convenience. The product used was analyzed for glucose by the Folin-Wu method, and the concentration was found to be as stated. It is, therefore, probable that errors arising through reliance upon commercially prepared glucose solutions are negligible.

After a few tests have been done, there is seldom any difficulty in obtaining the specimens in the manner given above. Two persons are needed to perform the test—one to insert the needles, give the glucose and take the samples—the other to keep the time, transfer the specimens into test tubes, oxalate the blood and rinse and dry the syringes.

For blood sugar estimations, the Folin-Wu method\* has been used.

*Nomenclature.* Since this test is a measure of the rapidity of the disappearance of injected glucose from the blood stream, it will be referred to as the *microinterval glucose clearance test*.

*Results. Results in Normal and Diabetic Persons.* The fasting, peak and 15-minute blood sugar levels in 65 metabolically normal individuals and 113 cases of diabetes mellitus are plotted in Chart 1. (Thirty-two of the latter were controlled on diets containing 150 gm. or more of available glucose without insulin.) The classification as "normal" or "diabetic" was made only after careful and generally prolonged clinical observation.

The most important diagnostic criteria of the curve obtained by the microinterval technique are: (1) the height of the "peak point," and (2) the 15-minute blood sugar level. The peak of the blood sugar curve was 175 mg. % or below in all but 3 of the "normals." One of these had a fractured femur, another a sciatic neuritis. The third had a pronounced psychoneurosis and showed a normal curve on repetition of the test. The 15-minute level was 125 mg. % or below in all but 4 of the normals. Two of these corresponded to the first 2 mentioned above, the third had migraine and the fourth was apparently healthy. Only 2 diabetics—both extremely mild—had peaks below 175 mg. % and none was below 125 mg. % at 15 minutes. Two diabetics (1 of whom had a low peak) had "borderline" 15-minute levels of 125 mg. % and 3 more had "borderline" peaks of 175 mg. %.

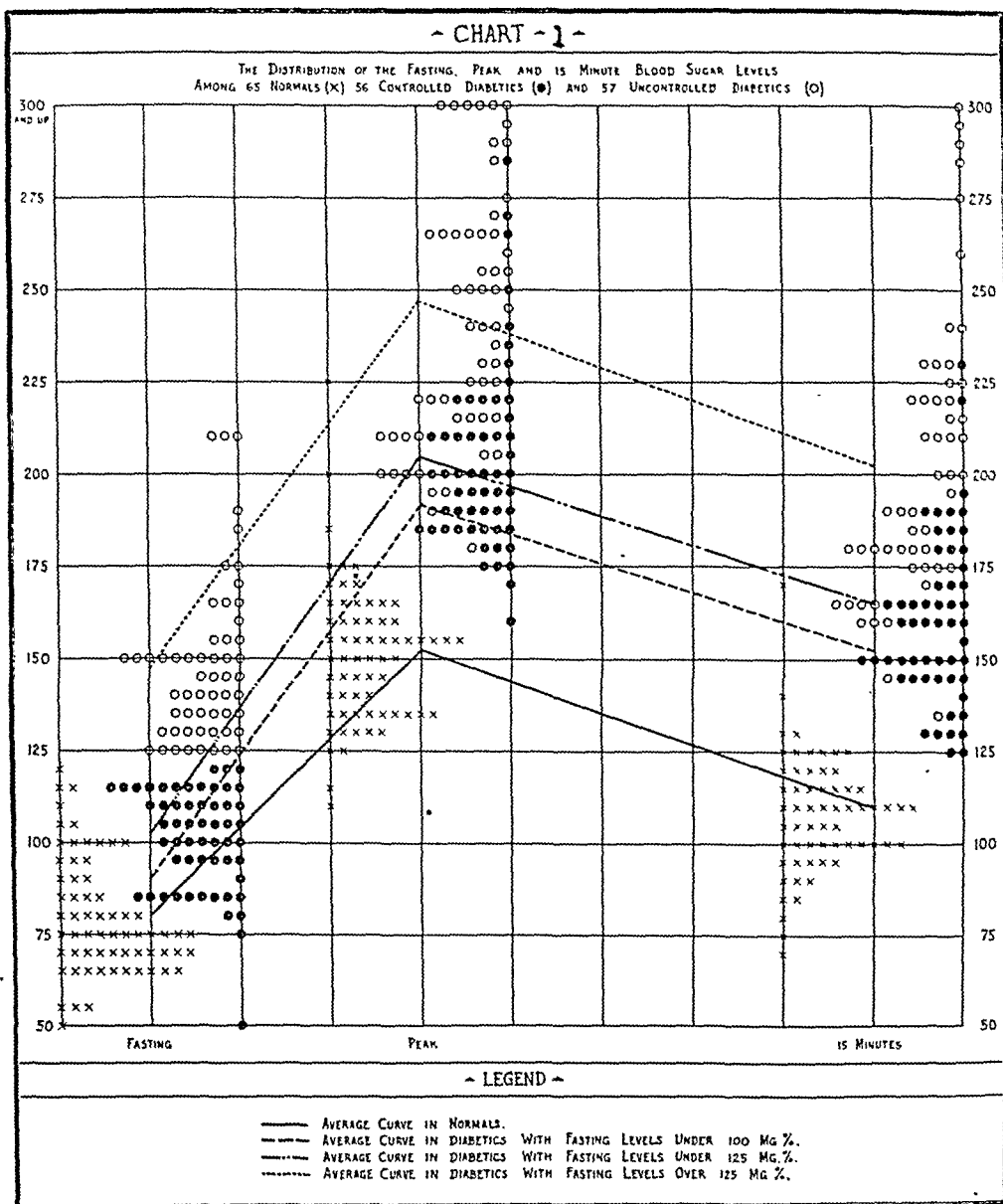
A diagnostic point of minor significance is the time at which the apex of the curve is reached. Fifty seven per cent of the normal and but 45% of the diabetic, group attained the peak by the 3d minute, the more severe the diabetes, the greater being the tendency toward a delayed peak.

In computing average curves, the diabetics have been divided into 3 groups: (1) Those with fasting blood sugars below 0.1%; (2) those with fasting levels below 0.125%; (3) those above 0.125% (Chart 1). The average fasting blood sugar of the 20 diabetics in Group 1 was only 5 mg. % higher than the mean initial level of the group of normals, whereas the average peak and 15-minute readings of the diabetics exceeded those of the normal by 39 and

\* That this method of blood analysis does not give true sugar values is of little importance, since the non-sugar reducing substances are constant and hence do not alter the shape of the curve. That this method is inaccurate with very high or very low blood sugars is likewise of little consequence in this test, since most of the readings are between 0.070% and 0.22%. In 59 duplicate determinations an average difference of 3.4 mg. %, and a maximal difference of 13 mg. %, in the two analyses were found.



44 mg.%, respectively. The composite curve of the diabetics of Group 2 exceeded that of the normals by 21 mg.% at the fasting level, 53 mg.% at the peak and 55 mg.% at 15 minutes. Thus it is evident that differences in the microinterval glucose clearance



curves of normals and diabetics are not merely reflections of differences already existent in the fasting levels.

Abnormal curves have been found in several conditions in which there was no clinical evidence of a coëxisting diabetes. Among these are cardiac decompensation with edema, hypertension, chole-

cystitis, peptic ulcer, hypopituitarism and chronic encephalitis, the curves of which will be presented and discussed in a subsequent communication.

Hence the microinterval intravenous method, like the oral test, is not specific for diabetes mellitus. The distinctive behavior of the diabetic as compared with the normal individual is quantitative rather than qualitative, and yet it is sufficiently striking in most cases to be diagnostic. A smaller dose of glucose (*e. g.*, 0.15 gm. per kg.) or calculation of the glucose dosage on the basis of surface area rather than body weight may diminish the number of "border-line" curves.

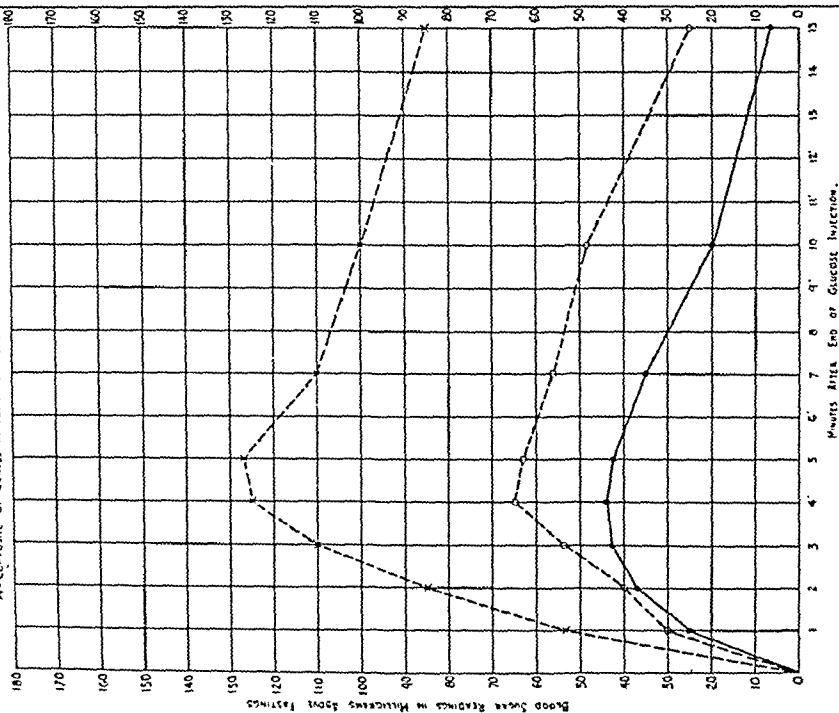
*Sources of Error.* 1. Dilution factor: In 15 cases, hemoglobin estimations (Sahli method) were made on each of the samples collected. The maximal dilution almost invariably occurred between the 4th and 6th minute, and in 13 of the 15 cases it ranged between 5.8% and 10% of the initial level. A case of polycystic kidney disease showed a 11.7% fall in hemoglobin, a case of polycythemia and hypertension, a 15.6% drop. Thus in the small series the error introduced through variations in the degree of dilution was generally less than 4% but in extremes was as high as 10%.

2. To investigate the possibility of an alteration in the flow of blood through the vein, due to the presence of the needle, a vein in the opposite arm was entered without applying a tourniquet and a specimen was taken simultaneously with one of those routinely collected during the course of the test. In 9 cases the average differences between the blood sugar readings in the 2 specimens was 2 mg.%, the maximal differences 6 mg.%, figures well within the limits of error of the Folin-Wu method of analysis. Since the results in these 9 cases so uniformly indicated that the needle did not interfere with the flow of blood through the vein, the series was not extended.

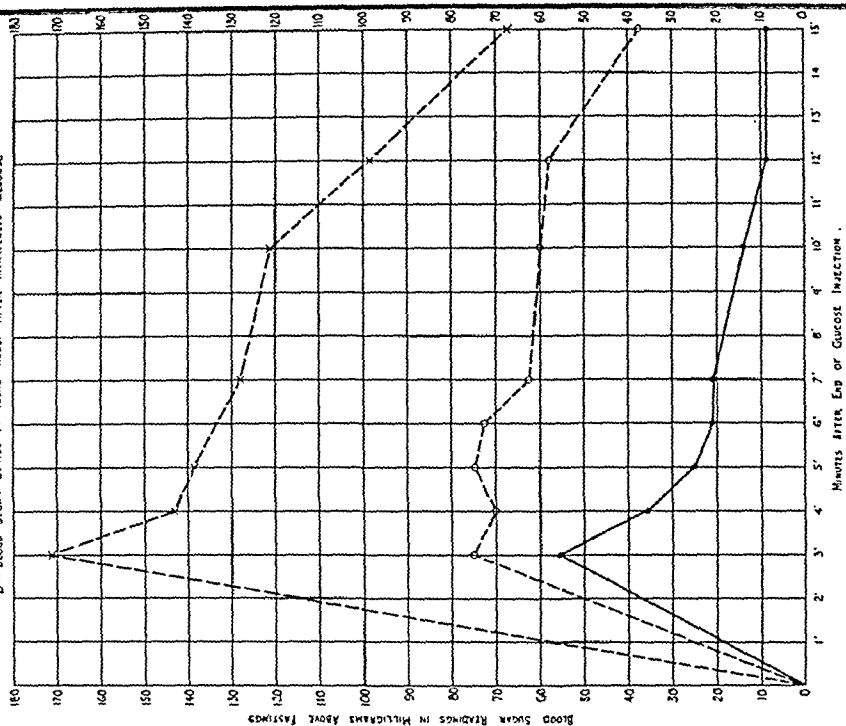
3. If glycogenolysis should occur in the liver during the course of the test, a serious error would result from the glucose liberated. Release of liver glycogen may well result from blood loss or from strong emotional stimuli. Since there was no appreciable change in blood sugar when specimens were taken in a similar manner after an injection of saline or alanin, the blood loss, in itself, is insufficient to provoke a hyperglycemia. Two patients were observed whose emotional state apparently affected the glucose clearance test. Both were very apprehensive and excited at the first test but placid at the second and showed high curves at the first test and normal ones on repetition. It is possible that undetected or less intense emotional stimuli affected the curves of many others to a lesser degree. If this were so, one would expect to find abnormal curves frequently in conditions characterized by emotional lability. In this connection, it is significant that 18 out of the 19 cases of hyperthyroidism had normal curves before operation

## - CHART - 2 -

A - Composite of Curves in Four Normal Dogs After Intravenous Glucose



B - Blood Sugar Curves in Young Adult After Intravenous Glucose



- LEGEND -

— 0.10 G per Kg Body Weight  
 - - - 0.20 G per Kg Body Weight  
 ... 0.30 G per Kg Body Weight  
 - · - 0.35 G per Kg Body Weight

- LEGEND -

— 0.10 G per Kg Body Weight  
 - - - 0.20 G per Kg Body Weight  
 ... 0.30 G per Kg Body Weight  
 - · - 0.35 G per Kg Body Weight

and 6 out of 7 in whom the test was repeated postoperatively showed curves almost identical with those obtained beforehand. The only exception showed a higher curve after than before operation.

**Comments.** *Comparisons of the Oral and Microinterval Intravenous Tests.* The advantages and disadvantages of the oral and microinterval intravenous tests have been summarized in Table 1.

TABLE 1.—COMPARISON OF THE MICROINTERVAL INTRAVENOUS AND THE ORAL GLUCOSE TOLERANCE TESTS.

<i>Criteria.</i>	<i>I.V. Test.</i>	<i>Oral Test.</i>
Amount of glucose given . . .	10 to 20 gm.	50 to 150 gm.
Effect on diabetic status . . .	None demonstrable	Occasionally upsets tolerance seriously.
Time required for test . . .	17 min.	2 to 4 hrs.
No. of venepunctures . . .	2	3 to 5 or more.
	Rate of injection uniform	Rate of intestinal absorption indeterminate.
Technical difficulties . . .	A good vein in each arm necessary—2 workers needed—experience with test required	None except venepuncture.
Value in the differentiation of normals and diabetics	Less overlapping in the curves of normals and mild diabetics with the intravenous than with the oral test.	
Agreement in repeated curves	Closer agreement in duplicate curves obtained by the I.V. method.	
Effect of previous diet . . .	None demonstrated	Pronounced.
Background . . .	Unphysiologic	Physiologic.
Functions involved . . .	Principally diffusion through capillary walls (?)	Sum total of gastric emptying, intestinal absorption, diffusion and oxidation of glucose and conversion into glycogen.

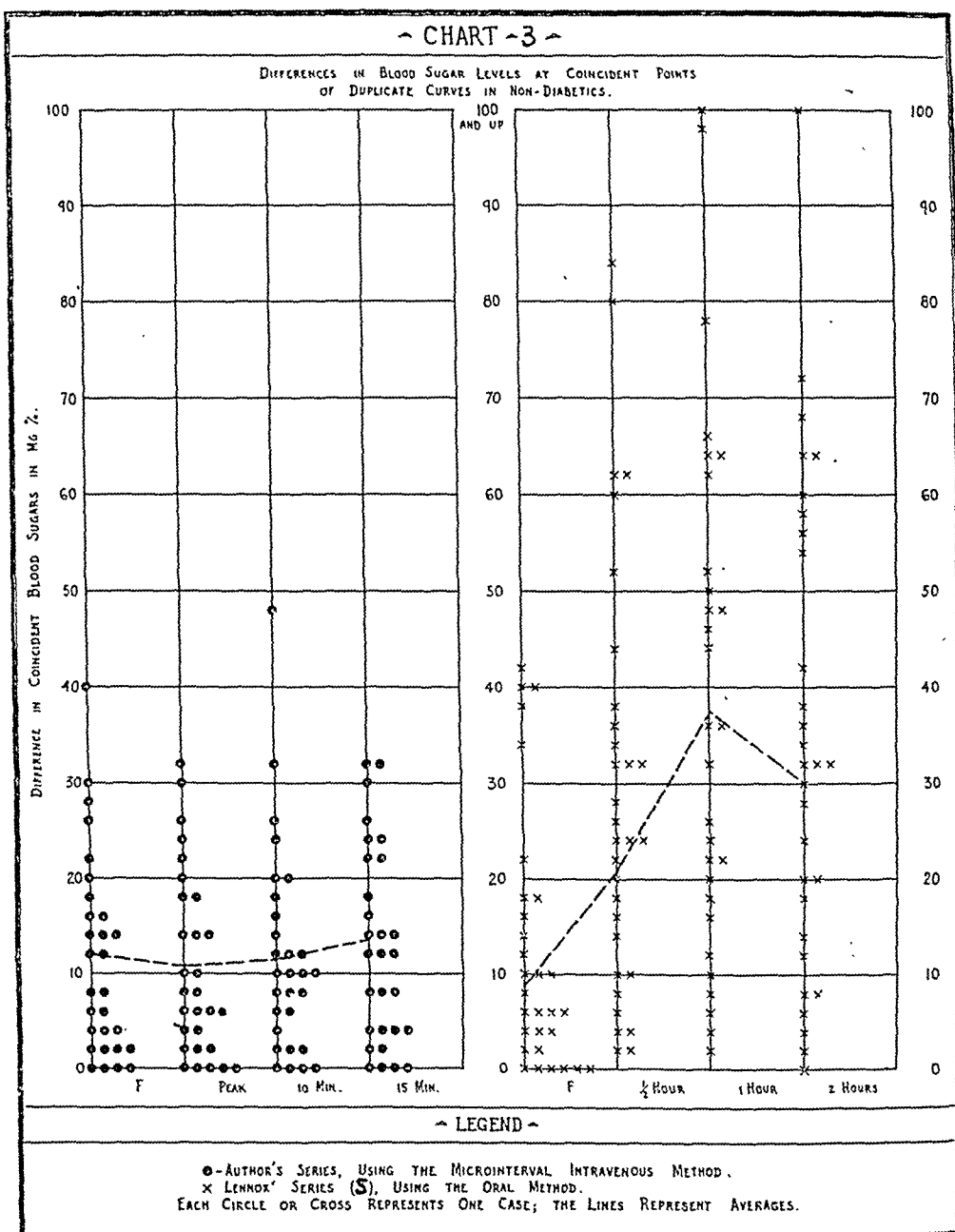
Lennox<sup>3</sup> compared the oral and intravenous tests in a considerable series and concluded that the curves obtained by the intravenous method "exhibit less variation from subject to subject and in the same subject less variation from time to time."

To test this point in regard to the method under discussion, 2 or more intravenous tests were made on a group of 31 non-diabetic individuals. In Chart 3, the differences in blood sugars at coincident points in the curves of each patient have been compared with those found by Lennox<sup>5</sup> in duplicate curves by the oral method.\* It would appear from these figures that repeated microinterval intravenous tests in the non-diabetic are in closer agreement than repeated oral tests.

Gray<sup>6</sup> warned of the danger of upsetting carbohydrate tolerance by the large doses of glucose generally given in the oral method. Beardwood's patient,<sup>7</sup> who was well controlled by diet alone before the oral test was carried out, showed a hyperglycemia and glycosuria on the same diet for 4 months afterward and for a time required 25 units of insulin daily. Many other examples of this situation

\* The curves of 2 patients who were very apprehensive during the first test were excluded from Charts 1 and 3.

could be added by those who have used oral glucose tolerance tests in diabetic individuals. The chief experimental evidence in support of these clinical observations lies in the work of Allen<sup>8</sup> on the



partially depancreatized dog. We have in no case observed reactions nor impairment of tolerance attributable to the glucose injected in the microinterval test.

Though the intravenous method for determining glucose tolerance is admittedly unphysiological, there is evidence to show that the passage of glucose through the liver prior to its entrance into the general systemic circuit makes little difference in the resultant blood sugar curves. McLeod and Pearce<sup>9</sup> injected glucose at a uniform rate into the superior mesenteric vein of dogs, took simultaneous specimens from the portal vein and inferior vena cava and found parallel curves after the first 2 minutes. Grafe and Meythaler<sup>10</sup> injected 5 cc. of 60% glucose into the femoral artery and into either the portal vein, hepatic or splenic arteries of the same dog on different days but under otherwise similar conditions. They took specimens from the ear capillaries and obtained closely comparable curves.

*Fate of the Injected Glucose.* The curves obtained by the microinterval method furnish an additional example of the rapid disappearance of intravenously injected glucose from the circulation. If the vascular system were impermeable to glucose, the injection of 0.2 gm. per kilo would raise the blood sugar from a fasting level of 0.1 mg. % to a plateau at 0.35 to 0.375 mg. %. Since the blood sugar generally does not rise above 175 mg. % in the normal and approaches the fasting level within 15 minutes, one may infer that the removal of the injected glucose begins at once and is almost complete in 15 minutes.

The following explanations for the disappearance of the injected glucose have been offered: (1) Conversion in the blood stream into a non-reducing substance; (2) excretion in the urine; (3) simple diffusion into the tissues; (4) conversion into glycogen; (5) oxidation.

1. By determining the total carbon content of the blood before and 2 minutes after the intravenous injection of glucose, Kurokawa<sup>11</sup> proved that the glucose did not remain in the blood stream in a non-reducing form but actually escaped into the tissues.

2. Though not routine, a sufficient number of urine examinations have been made during the course of the microinterval test to show that glycosuria is absent or negligible in normal individuals.

3. Most workers have attributed the rapid disappearance of glucose from the blood stream to simple diffusion into the tissues. Palmer<sup>12</sup> and Folin, Trimble and Newman<sup>13</sup> have found a substantial increase in the sugar content of various tissues, particularly the skin, shortly after the intravenous injection of glucose. Urbach and Sicher<sup>14</sup> and Trimble and Carey<sup>15</sup> found that the skin sugar concentration in relation to the blood sugar was appreciably higher in fasting diabetics than in fasting normals. Thus one might infer that, due to its higher sugar concentration, diabetic skin (and probably other tissues as well) may be less capable of removing added sugar from the blood stream than normal skin. Though differences in the gradient of diffusion may partially, if not wholly, account for the immediate divergence in the curves of normals

and diabetics, it seems unlikely that they are alone responsible for the differences in the latter parts of the curves.

4. There is as yet no analytical method sufficiently sensitive to be applicable to the study of the changes in tissue glycogen in the first 15 minutes after the injection of the relatively small amount of glucose used in this test.

5. Oxidation of glucose in the tissues has been studied by changes in the respiratory quotient. Since fluctuations in the respiratory quotient occur in fasting individuals and since a slight rise may be caused even by the act of drinking, changes of less than 0.05 have not been considered significant. Many workers<sup>16</sup> have found the first significant rise in R.Q. from 30 to 60 minutes after the oral administration of glucose. Similar results after intravenous injection were obtained by Bernstein and Falta<sup>17</sup> in man and by Ritlop<sup>18</sup> in dogs. Thus we may conclude that oxidation of glucose in the tissues is not demonstrable by present methods during the first 15 minutes after its administration.

There is evidence to show that administration of insulin prior to the injection of glucose expedites both the rise in R.Q. and the disappearance of the glucose from the blood stream. Ritlop found a much earlier response of the respiratory quotient to injected glucose when insulin was given prior to the glucose. Elias, Guedemann and Roubitschek<sup>3</sup> made duplicate intravenous tests in one of which 5 units of insulin were given 45 minutes before the glucose. The fasting level was not appreciably changed by the preliminary dose of insulin but the peak attained 5 minutes after the glucose injection was distinctly lower and the return to the fasting level more rapid.

Increased insulin activity is demonstrable in the blood in the pancreatic vein soon after the intravenous injection of glucose. Zunz and LaBarre<sup>19</sup> transfused blood from the pancreatic vein of 1 dog into the jugular vein of another for a period of 20 to 30 minutes and found no change in the blood sugar of the recipient. They then injected 60 cc. of 20% glucose intravenously into the donor during the blood transfusion and found a marked fall in the blood sugar of the recipient at the end of the transfusion. In a control experiment with the vagi of the donor severed, no change occurred in the blood sugar of the recipient.

Whether insulin is liberated rapidly enough from the pancreas to appreciably influence the disposal of glucose during the first 15 minutes after sugar injection is still a matter for conjecture. Reasoning from this premise, however, one might explain some of the differences between the normal and diabetic curves by the presence of an intact or impaired islet function.

**Summary.** Twenty-four intravenous glucose tolerance tests have been collected from the literature of the past 20 years and constructively criticized. A modification has been offered which is carried out, in brief, as follows: A vein is entered, a fasting speci-

men taken and glucose to the amount of 0.2 gm. per kg. body weight is injected at a uniform rate in exactly  $1\frac{1}{2}$  minutes. Within the next 3 minutes a vein in the opposite arm is entered and specimens are collected exactly 3, 4, 5, 10 and 15 minutes after the end of the injection. Since this test is primarily a measure of the rapidity of disappearance of injected glucose from the blood stream, it is referred to as the *microinterval glucose clearance test*.

In comparison with the oral and most of the intravenous tests, the method proposed in this communication has the following advantages: (1) A uniform rate of introduction of glucose into the blood stream is assured; (2) only 2 venepunctures are required; (3) the test is completed in 17 minutes; (4) a smaller amount of glucose is used; (5) repeated tests on the same individual are in closer agreement.

The results in 65 normal individuals and 113 cases of diabetes mellitus are presented. The most important diagnostic criteria of the curve are the height of the peak point and the 15-minute blood sugar level. The apex of the blood sugar curve was 175 mg. % or below in all but 3 of the normal group and the 15-minute level was 125 mg. % or below in all but 4 normals. Only 2 diabetics—both extremely mild—had peaks below 175 mg. % and none was below 125 mg. % at 15 minutes. In 2 diabetics, however, the 15-minute reading was exactly 125 mg. % and in 3 others "borderline" peaks of 175 mg. % were obtained.

We feel that a "normal" microinterval curve (peak of 175 mg. % or below and 15-minute level of 125 mg. % or below) is strong presumptive evidence against the presence of diabetes mellitus. On the other hand, an abnormal curve is not of equal diagnostic significance. Curves similar to those obtained in diabetes have been found in several other conditions, such as cardiac decompensation, hypertension, cholecystitis, peptic ulcer, carcinoma and chronic encephalitis.

The fate of the injected glucose has been conjectured and an attempt has been made to explain the early appearance of a distinctive response in normals and diabetics.

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## THOMSEN'S DISEASE.

### (MYOTONIA CONGENITA.)

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CONGENITAL myotonia was first adequately described (1875) by J. Thomsen,<sup>1</sup> a Danish physician, himself a sufferer from the disease, and in whose family the disease was noted for five generations. It

had been observed previously by Bell (1832), Benedikt (1864), and von Leyden (1866). The name of myotonia congenita was attached to the disorder by Strümpell. Jelliffe and Ziegler<sup>2</sup> have recently reviewed 20 cases of congenital myotonia which had appeared in the American literature up to 1932.

The disease usually appears in several members of a family in successive generations. In most of the recorded cases, it has existed in several relatives of the patient, generally in one of the parents, and in the patient's brothers, sisters, and children. Many of Thomsen's ancestors are said to have suffered from mental weakness.

It appears in both sexes, but more commonly in the male. Koch<sup>3</sup> found 91 of 102 collected cases to be in men. Symptoms are noticed very early in life, and the disease tends to persist with varying intensity throughout life. When the patients are first seen, they are usually about 20 years old, or less, and have had the disease as long as they can remember; or, it may have been first noticed in childhood when athletic activity was restricted because of muscular stiffness.

The main features are a disturbance of muscular activity such that at the beginning of a voluntary movement excessive tonus of the muscles involved renders the movement slow and difficult. When a movement has been repeated several times, this excessive tonus subsides, and the movement is performed in the normal way. A period of rest, however, is quickly followed by a return of the difficulty. The disturbance is usually most conspicuous in the muscles of the arms and legs.

The peculiarity of motion occurs only in voluntary movements. Muscular contractions are slower than normal, and the muscles involved remain more or less contracted for some seconds. The contraction is so powerful that the antagonistic muscles cannot overcome it. If a voluntary movement is repeated several times, the patient begins to perform each movement before the preceding contraction has been completely relaxed, and his difficulty as regards the stiffness gradually diminishes in each movement.

White<sup>4</sup> sums up the difficulty quite well: Flexion of the fingers usually illustrates the peculiarity of the disease; it is obvious that the flexor muscles contract more slowly than normally; they appear to remain completely contracted for from 1 to 3 seconds, and then are not at once completely relaxed, for if the patient is told to open the hand as quickly as possible, it is often between 7 and 10 seconds before the extensors completely overcome the flexors. If flexion be repeated as rapidly as possible, the second contraction obviously occurs more rapidly than the first, the third more rapidly than the second, and after about a half dozen contractions, the action appears quite normal. The difficulty is the same whichever muscles are affected, and different patients find different movements particularly difficult.

Such a defect has never been recorded in the acts of swallowing,

respiration, micturition, defecation, or parturition. With these exceptions, the stiffness may be observed in any movement executed by voluntary muscles. No reports of any sensory disturbance in this disease have been found, and the optic disks, when examined, have appeared healthy.

The characteristic alterations found in the electrical reactions are as follows:

1. Mechanical stimuli to motor nerves: no increase in irritability.
2. Faradic current to motor nerves: quantitatively normal; with strong current, the contraction produced on closing the circuit lasts much longer than normally.
3. Galvanic current to motor nerves: same as with faradic current.
4. Mechanical stimuli to muscles: contractions induced more easily than in health; contractions may last from 5 to 30 seconds.
5. Faradic current to muscles: if strong current, contraction lasts from 5 to 30 seconds.
6. Galvanic current to muscle: K.C.C. and A.C.C. are equally easy to obtain (in health, K.C.C. is much more readily elicited than A.C.C.).

In general it may be said that the contraction induced in muscles of individuals with Thomsen's disease lasts longer than in normal persons even when weak currents are used, and that with strong currents, the contraction lasts some seconds and relaxes quite slowly. The same patient does not usually exhibit all of the features of the electrical reactions usually classed as characteristic of this disorder.

The usual pathologic picture is marked hypertrophy of the affected muscles, which are firmer than is normal tissue when in action. Microscopically, the muscle fibers are usually considerably hypertrophied, some being 2 to 4 times the normal size; it is reported that, on cross section the bundles of fibrillæ, instead of having the normal polygonal form, are much rounder than normal, some being almost circular. Longitudinal sections may reveal an increase in the number of muscle nuclei.

The disorder is essentially chronic, usually progressively increasing up to puberty, or even later. Relapses and remissions are not uncommon. Instances of complete recovery have not been reported, although the disease does not of itself lead to death.

**Case Report.** The patient (No. 33-14701), a white male, aged 19, was admitted to Dr. Stengel's ward in this hospital, complaining of stiffness of numerous joints and muscles. As long as he can remember the patient has had some difficulty in the initiation of muscular movements of all parts of the body. This was not especially troublesome, however, until the age of 15, but during the past 4 years has become progressively worse.

Movements cannot be initiated as rapidly as in the normal individual but must be begun slowly, as though there were a partial inhibition of action when first undertaken. After a particular movement has been performed several times, the involved muscles seem to respond better and soon the

motion can be performed as rapidly as normally. Following a rest period of several minutes, initiation of movement is again slow; for example, the patient cannot arise from a chair and immediately begin to run. He must start by walking slowly, then walk fast, then trot, and finally can run as fast as his classmates. He described nothing abnormal concerning his sensation of motion. The only other symptom of which the patient is aware is excessive hidrosis, which has been present since childhood. No loss of weight has been noted.

Both the father and a younger sister are troubled with a similar condition, but to a lesser degree. The sister has in addition a tendency to soreness and pain in the muscles and joints. The mother and brother of the patient and other relatives, so far as is known, are free from any similar complaint, nor is there a reliable history of the condition in earlier generations.

His past medical history is negative. He is a senior in high school, and engages in athletics. However, during the rest periods in any athletic contest, he must be in motion continuously to avoid developing stiffness in the various muscles.

Upon physical examination he was found to be a quite heavily muscled lad weighing 167 pounds stripped, 68 inches in height without shoes, intelligent and coöperative. Upon exertion of the slightest degree (such as slow walking), his face was bathed with droplets of perspiration and the skin became very pink. Examination of the heart, lungs and abdomen was essentially negative. Peripheral reflexes (biceps, triceps, patellar and Achilles) were normal.

Initiation of movements was definitely retarded and all motions were begun quite slowly. After repetition these gradually became faster. The disturbance was most marked in the extremities. After rising from a chair, the patient could not begin to take a forward step for several seconds and then advanced very slowly and "stiff-leggedly." After a half dozen steps he could walk normally. Difficulty in initiating motion was most marked when the antagonistic muscles had been contracted strongly. For example, voluntary motion at the elbow was quite free if the range of motion was not great and if there was an effort to keep the limb relaxed. However, if the patient strongly flexed his forearm on the upper arm he could subsequently extend it only slowly and with effort. After grasping the examiner's hand tightly, the patient could open his hand only with great difficulty; however, after repeating this several times, he performed this motion easily and quickly.

Among the routine laboratory studies, the following were normal: complete blood count, urinalyses, blood Wassermann with all antigens, blood urea nitrogen, blood sugar, serum calcium, phosphorus, and protein and the electrocardiogram. His basal metabolic rate was  $-14\%$ . The therapeutic effect of 25 gm. of glycine continued daily for 7 days was tried but no beneficial results were noted, and 24-hour specimens of urine showed no creatin during the period of administration. This occasioned no surprise in view of the dissimilarity between this condition and the forms of myasthenia and muscular dystrophy in which benefit has been reported from glycine therapy.

A biopsy, taken from the left gastrocnemius muscle, was examined by Dr. E. B. Krumbhaar and compared with a similar specimen from a supposedly normal individual of the same age and sex. His report is as follows: "As compared with a slide of a normal gastrocnemius (boy of 22, PGH. Aut. 24731, October, 1934), the loss of compactness of each fiber is striking. The cross striations are very faint, the longitudinal fibrilli very prominent, often shredded out, with no visible sarcolemma, so that boundaries of the muscle fiber occasionally cannot be determined. The size of the longitudinal

cut fibers is somewhat larger than normal—an average measurement of 20 of each gives a diameter of  $68\ \mu$ , *vs.*  $52\ \mu$  of the normal. The difference in size is more marked in the cross-section (Figs. 1 and 2) which also shows the 'shredding' effect, the average area of 20 fibers being more than twice that of 20 normal fibers (diam.  $76\ \mu$  *vs.*  $54\ \mu$ ). A minor factor in this increase is the increased space between the fibrils. The muscle nuclei did not seem to be increased. Schiefferdecker's (*Deut. Ztschr. f. Nervenheilk*, 25, 1, 1903) droplets or granules were not seen. The section is certainly not normal muscle tissue."

Electrical reactions, performed by Dr. M. J. Cooper, revealed in the right anterior thigh muscles an increased muscular irritability to faradic current and some increased irritability to galvanic stimulation. The contraction of the muscle was strong but its relaxation was distinctly slow and gradual. A.C.C. was approximately equal to K.C.C. In the left anterior thigh muscles, similar but less distinct reactions were obtained; in the calf and peroneal muscles on each side there was increased faradic irritability, A.C.C. being approximately equal to K.C.C., but no distinct sluggishness of relaxation after electrical stimulation of these muscles was manifest. The excitability of the nerve trunks of the lower limbs was approximately normal. The muscles of the upper limbs showed very little abnormality in the response to electrical stimulation, except the posterior part of the right deltoid, which exhibited a slowness of relaxation after tetanic contraction to faradic stimulation, and the intrinsic muscles of the hands, which showed a slight reduction of electrical excitability, and some sluggishness both of contraction and relaxation.

Various muscles (left triceps and biceps, and right gastrocnemius) were tested with needle electrodes by Dr. G. Gammon. It was found that at the beginning of voluntary movements, especially if forced, a spasm resulted which could not be voluntarily relaxed. This contraction of the muscle was accompanied by normal action currents, and the failure to relax was not due to any weakness of the opposing muscles which were put into use to straighten out the limb. The action currents outlasted the patient's knowledge of contraction. Repetition of the movement rapidly resulted in failure of appearance of the spasm. No action currents were present when the muscle was not in spasm. The effective spasm was present even though the opposing muscle was not thrown into play. No studies were made on obtaining the phenomenon by reflex action. All of the muscles studied showed this same effect. These action potentials are to be interpreted as arising from the contracting muscle and not from its nerve supply. One cannot definitely determine from these whether the origin of the spasm is nervous or muscular.

NOTE.—Since this article was written, the patient was placed on ephedrin sulphate, gr.  $\frac{2}{3}$  t. i. d. by mouth, with marked subjective improvement.

**Discussion.** This case seems worthy of report because of the paucity in the American literature of accounts of families with this disease, and because of the unfamiliarity of many internists with the clinical picture. In fact, this patient had been treated elsewhere over a period of years with a diagnosis of arthritis because of his chief complaint of stiffness of the muscles and joints. The outstanding feature of the disease is the stiffness of voluntary movement on effort. The myotonia may become much more marked under emotional stress or exposure to cold. Warmth is said to decrease the tone.

Various hypotheses have been advanced concerning the nature of

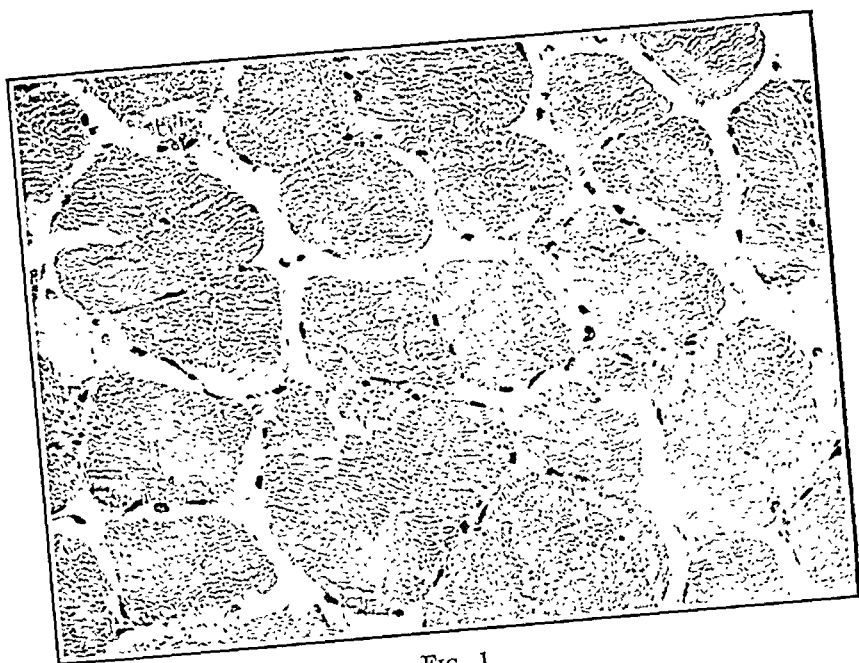


FIG. 1

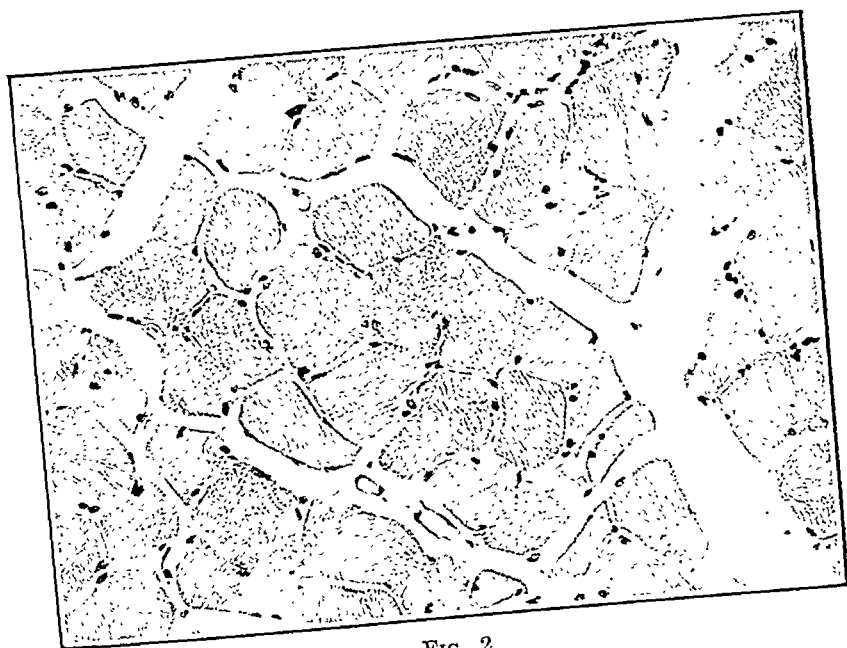


FIG. 2



the disorder; these include a myopathy, disease of the sympathetic nervous system, endocrine dysfunction, and a parasympathetic disturbance of muscle tone in some way related to endocrinopathy (especially the thyroid or parathyroid glands).<sup>6</sup> It has been reported<sup>7</sup> that the individual muscle fibers possess an excessive proportion of undifferentiated sarcoplasm, which latter in contrast to the fibrillar element of muscular tissue, is said to contract and relax with a slow muscle wave, thus accounting for the sluggish contraction and relaxation seen in this condition.

Conditions sometimes confused with Thomsen's disease include paramyotonia congenita, amyotonia congenita, myotonia atrophica, and progressive muscular dystrophy. The tonic spasms occurring in the voluntary muscles in paramyotonia congenita (Eulenberg's disease) are induced by exposure to cold, and not by exertion. They are most commonly found in the face, and may persist for 10 to 15 minutes. Amyotonia congenita (myatonia congenita, Oppenheim's disease) is characterized by extreme flaccidity of muscles with diminished electrical excitability to faradic and galvanic current. The extremities can often be placed in all sorts of abnormal positions of hyperflexion or hyperextension without pain or discomfort. Myotonia atrophica is probably closely related to Thomsen's disease, occurring usually after the twentieth year, and in which general wasting is a conspicuous feature. Cataract is frequently found in families of the patients.<sup>5</sup> Pathologically the muscle fibers appear quite small, but contain all the markings of normal muscle tissue.<sup>8</sup>

Under the heading of progressive muscular dystrophy (myopathies) is considered a number of muscular disorders probably not of spinal origin. They differ from the true muscular atrophies according to Spiller<sup>9</sup> in that they are hereditary or familial, they begin early in life, there is usually involvement of the trunk, pelvic or shoulder girdle muscles before the distal portions of the extremities, no true reactions of degeneration are present, and there are no fibrillary tremors. Of the more important subdivisions of the myopathies, three may be mentioned: the muscular pseudohypertrophy which affects chiefly the calves, and is accompanied by atrophy of the muscles of the thighs, back, shoulder, scapula, and of the calves themselves at a later date. Second, there may be noted the juvenile form (Erb's type) in which the hypertrophy is noted especially in the muscles of the shoulder and pelvic girdles. Third, there is the Landouzy-Dejerine or facio-scapulo-humeral form in which no hypertrophy is usually seen, but in which atrophy begins in the face and shoulder girdle muscles. In the myopathies, Grinker states that the essential pathologic process is a large degree of swelling of the muscle fibers, with breaking up of the striations and the appearance of large fatty vacuoles in the sarcoplasm.



**Summary.** 1. A case of congenital myotonia (Thomsen's disease) is presented with a short résumé of the important features of this disorder.

2. Biopsy section of the affected muscle is presented.

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## BOOK REVIEWS AND NOTICES

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**DISEASES OF THE MOUTH AND THEIR TREATMENT.** A Text-book for Practitioners and Students of Medicine and Dentistry. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc. DR. MED. DENT., Professor of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, University of Pennsylvania, and SIGMUND S. GREENBAUM, B.S., M.D., Associate Professor of Dermatology and Syphilology in the Graduate School of Medicine of the University of Pennsylvania. Pp. 602; 287 illustrations and 11 colored plates. Philadelphia: Lea & Febiger, 1935. Price, \$9.00.

THERE is everything to praise and little to criticize in this book. It is well bound, printed on glossy paper and the illustrations are abundant and excellent. The treatise begins with anatomy and physiology, continuing with methods of examination of the oral cavity and followed by generalities as to symptomatology of disease of the mucous membranes, teeth and gums as well as oral hygiene and dental prophylaxis. After these preliminaries the special disease entities of the mucous membranes as well as of teeth and related areas of the skin of the face are dealt with individually and systematically. Particular emphasis is placed on pathology. It is difficult to understand how any dentist or physician, particularly the dermatologist, could do without this volume. F. W.

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**TO REMIND: A BIOLOGICAL ESSAY.** (The Abraham Flexner Lectures, Series No. 2.) By SIR WILLIAM BATE HARDY, M.A. (CANTAB.), F.R.S.; HON. D.Sc. (OXON.), HON. LL.D. (ABERDEEN, EDINBURGH, BIRMINGHAM), Fellow of Gonville and Caius College; Director of Food Investigation, Department of Science, Industrial Research, etc. Pp. 45. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, \$1.00.

THE second series of the Abraham Flexner Lectures in the School of Medicine of Vanderbilt University was delivered in February and March, 1931, by the late Sir William Bate Hardy. At the time of his death only the two lectures here published had been prepared for publication: a charming philosophic speculation on the riddle of life as exemplified in the fundamental living substance: protoplasm, and the asymmetry of molecular structure in living matter. R. K.

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**THE PRINCIPLES OF THERAPEUTICS.** (The Abraham Flexner Lectures, Series No. 3.) By FRANCIS RICHARD FRASER, M.A. (CANTAB.), M.D. (EDIN.), F.R.C.P. (LOND.), Professor of Medicine in the University of London. Pp. 135. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, \$2.00.

THE third series of the Abraham Flexner Lectures, delivered in 1933, in the School of Medicine of Vanderbilt University, in which Professor Fraser discusses for his student hearers the principles which underlie the rational treatment of disease, using as his texts: historic consideration of the development of therapeutics; the treatment of the causes of disease; treatment based on symptoms; the care of the patient. This little book should be read by all senior students. R. K.

**POLIOMYELITIS.** A Handbook for Physicians and Medical Students. By JOHN F. LANDON, M.D., Attending Physician, Willard Parker Hospital; Special Consultant in Pediatrics, Woman's Hospital, New York, etc., and LAWRENCE W. SMITH, M.D., Pathologist, Willard Parker Hospital, etc. With a Section on the orthopedic after-care of the disease by GARRY DEN. HOUGH, JR., M.D., F.A.C.S., F.A.A.O.S., Attending Orthopedic Surgeon, Shriner's Hospital for Crippled Children, Springfield, Mass. Pp. 275; 18 illustrations. New York: The Macmillan Company, 1934. Price, \$3.00.

"THE 1931 New York City epidemic of poliomyelitis afforded the authors an unusual opportunity to observe an exceptionally large amount of clinical and pathological material . . . . Approximately 1000 cases were admitted to the Willard Parker Hospital during that summer and 81 autopsies were performed . . . . These and some 1400 additional cases occurring in the other communicable disease hospitals of the Department of Hospitals have been exhaustively studied . . . . It is the aim and hope of the authors to present in this short volume a well rounded and compact exposition of the disease, . . . . including an unbiased evaluation of serum therapy, the use of the respirator, the after care, etc., which will enable the general practitioner and the student to obtain a practical working knowledge of the disease." The authors have achieved their aim: the book is a well-balanced, concise, accurate presentation of the subject. Also worthy of mention are the appendices, describing the nursing care of poliomyelitis, the aseptic technique used in the Willard Parker Hospital, and the New York City Health Department regulations concerning this disease.

R. K.

**FOOD AND HEALTH.** By HENRY C. SHERMAN, Mitchill Professor of Chemistry, Columbia University. Pp. 296. New York: The Macmillan Company, 1934. Price, \$2.50.

THE best presentation of practical dietetics for the well, who would remain so, that has come to the knowledge of the Reviewer. "This book is not written by a physician nor for those who are ill; it is for those who wish to maintain and enhance their health, and the health of any others for whose food selection they may be responsible." The writer's distinguished achievements in the field of the chemistry and physiology of nutrition eminently qualify him to present the subject. This he has done in a clear, lucid manner, and from a sound conservative viewpoint. Written for the intelligent layman, the book always preserves a scholarly and scientific tone, not falling into the "journallese" style of so many medical books for lay consumption. It is warmly recommended to all readers, lay and medical, who wish an accurate, concise and practical exposition of our present-day knowledge of food and its relation to health.

R. K.

**THE NEW-BORN BABY.** A Manual for the Use of Midwives and Maternity Nurses. By ERIC PRITCHARD, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Medical Director, Infants Hospital, London; Pediatrician to Queen Charlotte's Maternity Hospital, etc. Pp. 272; 9 illustrations. London: Henry Kimpton, 1934. Price, 4/6.

THIS little book is simply and plainly written and contains adequate information for nurses specially trained in obstetrics or for midwives. All books of this type probably err on the side of presenting too much provender for partakers of the fare. One notes slight differences of opinion as to the use of certain materials and which may be common practice in England.

For instance, the author feels that any artificial food containing cow's milk should be peptonized before being offered to a new-born infant. In the United States we are apt to feel that boiling, or acidification, or both, modify the milk best.

The author unfortunately introduces a controversial matter that might well be omitted. He feels that pyloric stenosis is acquired and not congenital—that it is the end result of habitual vomiting. There are few who will agree with him.

S. T., JR.

**THE VITAMIN B REQUIREMENT OF MAN.** By GEORGE R. COWGILL, Ph.D., Associate Professor of Physiological Chemistry in Yale University. Pp. 261; 8 illustrations, 81 tables and 8 charts. New Haven: Yale University Press for The Institute of Human Relations, 1934. Price, \$4.00.

FROM data accumulated over a considerable period of research upon several species of animals (rat, pigeon, mouse and dog) and upon individuals of different size in the same species, Cowgill has derived a mathematical formula applicable to the vitamin B requirements of each species, the important variables in the calculation being weight, metabolism (calories) and maximum (or adult) weight. This formula he finds can be applied satisfactorily to the requirement of the human species.

The monograph reviews in detail the experimental work and the steps by which the formula was derived and confirmed. It includes also tables of foodstuffs in terms of their unit content of vitamin B and analysis of the vitamin/calorie ratio of diets known to have produced or to have failed to produce beri beri, as reported in the literature of various epidemics of beri beri. The predicted result of such diets in terms of their adequacy in vitamin B is compared with the actual result (*i. e.*, the presence or absence of beri beri).

The book is written in terms that any well-informed reader can understand. A considerable bibliography is appended.

E. W.

**AMERICAN MEDICINE.** By HENRY E. SIGERIST, The William H. Welch Professor of the History of Medicine, The Johns Hopkins University. Translated by HILDEGARD NAGEL. Pp. 316; illustrated. New York: W. W. Norton & Co., Inc., 1934. Price, \$4.00.

FROM the time of de Tocqueville just a century ago, some of the best evaluations of America have come from foreigners—not that we must any longer call Sigerist a foreigner, but such he was when this book was conceived during a tour of the country in 1931 and 1932. An account of the development of American medicine, this book opens with brief descriptions of Indian medicine, colonial times and non-medical United States, by way of background. The chapter on Pioneers, the longest in the book, carries us from John Morgan to Osler and the founding of the Johns Hopkins Medical School. In 56 short pages it gives in the author's graceful, sparkling style a fine bird's-eye view of a full century—the discovery of anesthesia, for instance, being presented from an obviously adequate knowledge of the subject. The chapters on Medical Education and Medical Science paint in swift bold strokes the lights and shadows of these developments, seen—as is perhaps natural—through Baltimore-tinted glasses. In the chapters on Physician and Patient, on Hospitals and Nursing, and on Preventive Medicine some of the social aspects of medicine in this country are touched upon in a way that is particularly illuminating, coming as it does at this time and from an accomplished historian and keen cosmopolitan observer, fresh on our scene. The extensive bibliography and indices testify to the large amount of ground covered; for an appreciation of the narrative charm, the book must be consulted at first hand.

E. K.

STAMMERING AND ALLIED DISORDERS. By C. S. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (ENG.). Pp. 182. New York: The Macmillan Company, 1935. Price, \$2.00.

CONSIDERING speech as a conditioned reflex, the writer theorizes that stammering results from faulty inhibition which "checks, quenches, blocks or impedes" vocalization. It is suggested that the male preponderance—four to one—may be due to a less stable conditioned reflex.

Primarily, the disorder shows partial inhibition; later, the child may become conditioned to various speech situations. If the stammering has begun abruptly, it may be aborted through rest and sedation. Failing in this, fatigue and excitement should be avoided and the more technical procedure, including "transquillization," "reënforcement" and "unconditioning" may be required. The text is lucid, the references abundant and the index informative. N. Y.

THE TECHNIQUE OF POSTMORTEM EXAMINATION. As Practiced in the Pathological Institute of McGill University at the Royal Victoria Hospital, Montreal. Compiled by D. R. COMAN, M.D., C.M., Assistant to the Instructor and Demonstrator in Pathological Anatomy. Pp. 47; 12 illustrations. Montreal: Renouf Publishing Company, 1934. Price, \$1.40.

A SMALL book on this subject, accurate and with adequate directions for performing necropsies, has long been needed to put into the hands of the pathological aspirant. Except for the translation of Virchow's booklet, "Postmortem Examinations," we know of none such in English. The present book, conveniently arranged with interleaved blank sheets, details the procedure used at the McGill Pathological Institute. In general, the technique is much like Virchow's. A few special procedures are added, together with a table of normal weights and a method for frozen section technique. With the increasing recognition of the value of necropsies in medical schools and hospitals, it is not too much to expect that every graduate of a first class medical school should have learned the technique and occasionally perform a necropsy—this booklet will show him how.

E. K.

DIE NEUROLOGIE DES 1.-7. JAHRHUNDERTS N. CHR. EINE HISTORISCH-NEUROLOGISCHE STUDIE. Sammlung Psychiatrischer und Neurologischer Einzeldarstellungen. Band VI. By DR. WALTER CREUTZ, Oberarzt an der Prov.-Heil- und Pflegeanstalt, Düsseldorf-Grafenberg und der psychiatrischen Klinik der medizinischen Akademie, Düsseldorf. Pp. 106. Leipzig: Georg Thieme, 1934. Price, M. 7.80.

NEUROLOGY has so recently become an independent specialty in medicine that its age-old history has not acquired much of a separate footing. This book is a praiseworthy attempt to sketch of the picture of classical neurologic knowledge during the first seven centuries of the Christian era, and of the seeds carried over through Arabian Medicine and the School of Salerno for the developments of the Renaissance and modern times. The first half of the book considers, with liberal excerpts, the neurologic contributions of Celsus, Soranus (Caelius Aurelianus), Galen, Aretaeus, Cassius, Oribasius, Aetius, Alexander of Tralles and Paul of Aegina. The latter half of the book assembles the neurologic knowledge of the period under the heading of Anatomy and Physiology, Paralysis, "Canina convulsio" (tic, facial palsy?), sciatica, lumbago, apoplexy, "Diminutio cerebri" (cerebral thrombosis?), epilepsy.

E. K.

## NEW BOOKS.

*Blood Groups and Blood Transfusion.* By ALEXANDER S. WIENER, A.B., M.D. Pp. 220; 41 illustrations and 72 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, \$4.00.

*Martini's Principles and Practice of Physical Diagnosis.* Edited by ROBERT F. LOEB, M.D., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University, and Presbyterian Hospital, New York. From the authorized translation by GEORGE J. FARBER, M.D. Pp. 213; 30 illustrations. Philadelphia: J. B. Lippincott Company, 1935. Price, \$2.00.

*Prassi Medico-Forense.* By PROF. DOTT. FRANCESCO BALLOTTA, Ainto e Docente nell'Institute di Medicina Legale della R. Università di Bologna. Pp. 167; 21 illustrations, some in colors. Bologna: Nicola Zanichelli, Editore, 1935. (Price not given.)

*The Cyclopedia of Medicine. Index to Volumes 1 to 12.* GEORGE MORRIS PERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS I. LEDERER, B.S., M.D., and A. GRAEME MITCHELL, M.D. Pp. 415. Philadelphia: F. A. Davis Company, 1934. Price, \$120.00 for set.

*The Dangerous Age in Men.* A Treatise on the Prostate Gland. By CHESTER T. STONE, M.D., Clinical Assistant Surgeon, Urologic Division, Bellevue Hospital, New York City; Urologist, Bergen County Hospital, Oradell, N. J.; Consultant Urologist, Rome State School, Rome, N. Y. Pp. 105. New York: The Macmillan Company, 1935. Price, \$1.75.

*The Patient and the Weather. Vol. II. Autonomic Dysintegration.* By WILLIAM F. PETERSEN. With the assistance of MARGERET E. MILLIKEN, S.M. Pp. 530, lithographed; 249 illustrations. Ann Arbor, Mich.: Edward Brothers, Inc., 1934. Price, \$6.50.

*International Clinics, Vol. I, Forty-fifth Series, 1935.* Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, Md., with 14 collaborators. Pp. 310; illustrated. Philadelphia: J. B. Lippincott Company, 1935.

Among the authors of the 9 medical and 5 surgical papers appear such well-known names as Wilder, Stroud, Haden, Musser, Grier Miller, C. C. Norris and Hans Hanke of Freiburg. The Recent Progress articles are by Cantarow on Cholesterol Metabolism, and by Goodwin and Balfour on Surgery.

*The Nervous Patient.* A Frontier of Internal Medicine. By CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University, Indianapolis. Pp. 453. Philadelphia: J. B. Lippincott Company, 1935. Price, \$4.00.

*A Manual of Biochemistry.* By J. F. MCCLENDON, Professor of Physiological Chemistry, University of Minnesota Medical School. Pp. 381; 58 illustrations. New York: John Wiley & Sons, Inc., 1934. Price, \$5.00.

## NEW EDITIONS.

*What You Should Know About Heart Disease.* By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School; Associate Attending Physician, New York Hospital, etc. Pp. 127; 4 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, \$1.50.

"Heart disease is now recognized as an important public health problem, as is evidenced by the growth of the numerous Heart Associations . . . The patient must understand his own condition if he is to coöperate in its cure and avoid the unpleasant results of the disease . . . The first purpose of this book is to help the patient to follow his physician's directions intelligently." (Publisher's note.)

*Physical Diagnosis.* By WARREN P. ELMER, B.S., M.D., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician to Barnes Hospital, etc.; and W. D. ROSE, M.D., late Associate Professor of Medicine in the University of Arkansas. Pp. 919; 342 illustrations. Seventh edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$8.00.

"The general form of the book has not been altered. New matter, especially on aortic murmurs, silicosis and diagnostic methods, has been added in order to make the work more complete and up-to-date. The sections on electrocardiography have been completely revised. Several new illustrations have been added." (From Author's Preface.)

*Diseases of the Skin.* By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.P.C.P. (EDIN.), Assistant in Dermatology, University of Kansas, School of Medicine. Pp. 1433; 1310 illustrations and 11 colored plates. Ninth edition, revised and enlarged. St. Louis: The C. V. Mosby Company, 1935. Price, \$12.50.

*Methods of Treatment.* By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, Kansas City General Hospital, etc. With chapters on special subjects by H. C. ANDERSSON, M.D., URSULLA BRUNNER, R.N., J. B. COWHERD, M.D., PAUL GEMPEL, M.D., H. P. KUHN, M.D., CARL O. RICKTER, M.G., F. C. NEFF, M.D., E. H. SKINNER, M.D., E. P. DEWEESE, M.D., and O. R. WITHERS, M.D. Pp. 879; 102 illustrations, Fifth edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$10.00.

*Useful Drugs.* A List of Drugs Selected to Supply the Demand for a Less Extensive Materia Medica, with a Brief Discussion of Their Actions, Uses and Dosage. Edited by ROBERT A. HATCHER, PH.M., Sc.D., M.D., and CARY EGGLESTON, M.D. Prepared under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 203. Ninth edition. Chicago: American Medical Association, 1934. Price, 60 cents.

*Physiology in Modern Medicine.* By J. J. R. MACLEOD, M.B., LL.D., D.Sc., F.R.C.P., F.R.S., Regius Professor of Physiology in the University of Aberdeen, Scotland, etc. Assisted in the present edition by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, EDWARD P. CARTER, Adjunct Professor of Medicine, Johns Hopkins University and Associate Physician, Johns Hopkins Hospital, J. M. D. OLMSTED, Professor of Physiology, University of California, J. M. PETERSON, Lecturer in Experimental Physiology, University of Aberdeen, and N. B. TAYLOR, Professor of Physiology, University of Toronto. Pp. 1154; 297 illustrations, including 7 plates in colors. Seventh edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$8.50.

*Diseases of the Rectum and Colon and Their Surgical Treatment.* By J. P. LOCKHART-MUMMERY, F.R.C.S. (ENG.), M.A., M.B., B.C. (CANTAB.). Senior Surgeon to St. Mark's Hospital for Cancer, Fistula and Other Diseases of the Rectum, etc. Pp. 605; 250 illustrations. Second edition. Baltimore: William Wood & Co., 1934. Price, \$10.00.

# PROGRESS OF MEDICAL SCIENCE

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## THERAPEUTICS

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UNDER THE CHARGE OF

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### THE TREATMENT OF HEART FAILURE AND ANGINA PECTORIS BY TOTAL THYROIDECTOMY.

THIS radical therapeutic procedure was first suggested by Blumgart, Levine and Berlin<sup>1</sup> less than 2 years ago. The genesis of the idea dates back to Levine's<sup>2</sup> observation of a single patient<sup>3</sup> upon whom a subtotal thyroidectomy had been performed in 1927 for the relief of chronic, intractable heart failure believed possibly to have been associated with latent or "masked" hyperthyroidism.<sup>4</sup> Despite the fact that the thyroid gland of this patient was found to be normal both grossly and microscopically, she recovered promptly from her congestive heart failure and remained well for 3 years. Thereafter mild congestive heart failure began to reappear and the patient succumbed to it 4½ years following the operation. The remarkable results obtained in this patient led to the trial of almost complete subtotal thyroidectomy as a means of relieving either intractable congestive heart failure or chronic, resistant angina pectoris in a small additional group of patients without clinical hyperthyroidism.

Study of these additional patients showed that while such subtotal thyroidectomy would cause a marked fall in the level of the basal metabolism, this reached its limit in a few weeks, after which it would return to normal or to the pre-operative level. Improvement in the cardiac symptoms was observed to be limited almost wholly to the brief period of lowered metabolic rate, the congestive failure or angina then promptly reappearing. These observations, when considered in conjunction with previous studies on the relation of the velocity of blood flow to the level of the basal metabolic rate,<sup>1</sup> led Blumgart to suggest the complete removal of the entire normal thyroid gland.



Accordingly, on December 15, 1932, the first operation for the complete therapeutic ablation of a normal thyroid gland was performed by Berlin<sup>1</sup> on a patient suffering from chronic rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation, the anginal syndrome and chronic intractable congestive heart failure. The immediate results were dramatic. All signs and symptoms of both the congestive heart failure and the angina disappeared during convalescence from the operation, and less than 4 months after operation the patient was working 8 hours daily without cardiac symptoms. On the basis of the striking benefits secured in this first patient more than a hundred patients have already been subjected to the procedure.<sup>6,7</sup>

**Theoretical Bases Underlying Total Thyroidectomy.** *Its Rationale.* With the development of more delicate and more accurate methods of investigation Blumgart<sup>6,8</sup> and his associates embarked upon an extensive series of studies of variations in the rate of blood flow in man in health and disease. They showed that in normal persons the rate of blood flow was directly determined by the metabolic demands of the body. These, in turn, were measured by the metabolic rate. Whenever the level of basal metabolism was elevated the velocity of blood flow was found correspondingly accelerated, if the circulatory system were normal. Uncomplicated hyperthyroidism was always accompanied by an increased rate of blood flow. Conversely, uncomplicated myxedema showed a diminished rate of blood flow. In each of these conditions the rise or fall in the velocity of blood flow was more or less directly proportional to the level of the metabolism.

The presence of heart disease was observed not to upset this established relationship between metabolic rate and velocity of blood flow so long as the heart disease was fully compensated. When congestive failure was present this relationship no longer existed and the rate of blood flow was retarded even when the basal metabolism was normal. In patients showing various degrees of congestive failure the retardation in the velocity of blood flow was more or less proportional to the severity of the cardiac failure. It was further observed that the rate of blood flow in myxedema was often as slow as that recorded in cardiac patients who were decompensated, yet the myxedematous patients were without evidences of circulatory failure. This observation led Blumgart to the deduction that, "The adequacy of a given speed of blood flow can be decided only in relation to the metabolic needs of the tissues."<sup>9</sup>

These and other related observations and considerations led Blumgart<sup>5</sup> and his collaborators to make the following statement: "The thought, therefore, arose that if the normal metabolic rate of the patient with congestive failure were reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of his body. In terms of the law of supply and demand, the supply of blood in such a patient with congestive failure would not be increased, but the metabolic demands of his body would be decreased to a level in conformity with his blood supply."

The modern conception of angina pectoris holds that the pain is due to the inadequacy of the coronary circulation in proportion to the work of the heart, that is, to the rate of cardiac metabolism. Total thyroidectomy, while not increasing coronary blood flow, may be expected through reduction in the metabolic rate of the heart muscle, to restore the bal-

ance between these two factors and thereby prevent the development of the attacks.\*

Support of the foregoing theory of the close relationships between the metabolic demands of the tissues and the production of heart failure of either the congestive or the anginal type is found in the clinical observations which have previously been recorded in patients with hyperthyroidism. Even as long ago as 1902, Kocher<sup>10</sup> observed and recorded the relief of congestive cardiac failure following subtotal thyroidectomy. This has, of course, been abundantly confirmed by others, especially by the extensive studies of Hamilton<sup>11</sup> and by the observation of the effects upon cardiac failure produced by diminishing basal metabolism in hyperthyroidism by the administration of iodine.<sup>12</sup> The reports by Morris<sup>13</sup> of the beneficial effects of subtotal thyroidectomy in a group of thyrotoxic patients having normal or subnormal metabolic rates are also of significant bearing. In contrast to them there stand, however, numerous reports recording the failure to influence cardiac and other circulatory symptoms by subtotal thyroidectomy performed on patients who were free from demonstrable thyrotoxicosis.

Approaching the problem from the opposite angle, there is a number of observations cited by Blumgart and his associates<sup>5</sup> in which the elevation of basal metabolism by the administration of thyroid to patients with myxedema was observed to produce attacks of angina pectoris and other symptoms of circulatory inefficiency.

#### **Selection of Cases for Further Study and Methods of Investigation.**

In order to put this radical therapeutic procedure to a thorough test and at the same time to avoid unnecessary risks cases were chosen with much care. Only such patients were selected whose prognoses for useful life were very doubtful or definitely poor. Yet no patient was selected who did not seem to be a fair surgical risk, or in whom the risks from the operation could not be made fair by pre-operative treatment. All patients with congestive failure had been under observation and treatment for considerable periods of time and all were such as could not be kept free from symptoms of failure when out of bed. Most, however, could be comfortable and without symptoms under treatment when bedfast. In every such patient any benefit which might follow total thyroidectomy could justly be ascribed to the operation. Similar rigid criteria were applied to the selection of patients with angina. Each patient was generally studied independently by several physicians before final decision. Blumgart says,<sup>5</sup> "No better gauge of the predicament of most of these patients could be found than their pathetic desire to hazard any of the dangers involved in order to secure possible benefit after having suffered for many years and after having observed their condition become progressively worse in spite of medical treatment."

A wide variety of types of cardiovascular disease was included in the group selected. There were cases with arteriosclerotic heart disease with angina, some with congestive failure, and some with hypertension

\* [Note: It is probable that the mechanism of the production of angina pectoris is not always so simple as this and involves one or more of several additional factors not the least of which appears to be the state of the central nervous system. —EDITOR.]

and paroxysmal dyspnea. Failure due to chronic rheumatic heart disease was included, both with and without auricular fibrillation. There was also right ventricular failure with cor pulmonale. Patients were rejected if they showed active rheumatic infection, recent vascular accidents, or were in the active stages of acute cardiac infarction from coronary thrombosis. Syphilitic cardiovascular disease was also rejected because of the known tendency of this form of failure to progress rapidly. All accepted patients were free from evidences of existing thyrotoxicosis, and none had a history of its previous existence. Postoperative study of the removed glands showed them to have been normal in every case but one. No physically immature patient was operated upon because of the risks of cretinism. Finally, no patient was accepted who could not give a clear and accurate account of his symptoms.

Every patient was subjected to detailed clinical investigation both before and after the operation. These studies were generally made independently by several observers, and often extended over many weeks prior to operation in order to minimize the operative risks by suitable treatment. This pre-operative clinical study also served as a basis for accurate comparison of the changes which followed operation. Many purely objective data were recorded routinely and as often as necessary both before and after the operation. These included determinations of the blood pressures, vital capacity, and body weight, all made under standardized conditions. Other data included teleoroentgenograms of the heart, electrocardiograms, photographs of the patient, frequent determinations of the basal metabolism, measurements of venous pressure, determinations of the arm to tongue circulation time as an index of the rate of blood flow, and studies of the patient's reaction to exercise as determined by the Master and Oppenheimer<sup>14</sup> test carried out under standardized conditions.<sup>15</sup> Finally in addition to routine blood chemical tests, studies were made on the level of the content of many constituents of the blood, especially phosphate, calcium and cholesterol.

**The Operation.** *Certain Precautions; Anesthesia.* The selection of the anesthetic which can be used in seriously ill patients with the smallest margin of risk is both difficult and of the utmost importance. At first gas and oxygen were employed, supplemented when necessary with small amounts of ether. However, among a comparatively small group of cases there were six deaths from postoperative bronchopneumonia for which the anesthetic was believed largely responsible. Avertin was abandoned after a stormy postoperative course in 1 case. Local anesthesia was then adopted at the suggestion of Mixer<sup>16</sup> with almost complete elimination of postoperative anesthetic mortality. The use of local infiltration anesthesia with procain was found to simplify the surgical technique by separating the tissue planes and rendering certain steps easier. All of the postanesthetic deaths occurred in cases with congestive failure; anginal cases have been shown to be better surgical risks. The infiltration carries with it the risk of transient paralysis of the recurrent laryngeal nerve. This can be avoided by not infiltrating along the tracheoesophageal sulcus or deeply into the gland.

Great caution must be observed not to damage the recurrent laryngeal nerve. The entire thyroid gland must be removed, and Berlin<sup>17</sup>

found in a series of 140 dissections that this nerve partially penetrated the gland in 10%. In 25% the nerve passed through the area of fixation of the gland to the trachea just below the anterolateral region of the cricoid bar at the level of the first and second tracheal rings—this is the so-called adherent zone. The dangers of laryngeal nerve paralysis can be avoided by remembering these two abnormal locations and by always identifying the nerves and preserving them intact by painstaking blunt dissection. Of the nerves dissected 65% were found to be safely placed in the sulcus between the trachea and esophagus where they were well protected against operative injury.

It was found possible further to insure against the dangers of recurrent nerve damage and paralysis by observing the simple precaution of careful laryngoscopic examination<sup>18</sup> before operation and again after the dissection of one lateral lobe of the gland had been completed. This required interruption of the operation for but a few minutes. If such examination showed paralysis of the homolateral vocal cord, the operation was then terminated. If the nerve were proved to be uninjured then the operation could be successfully completed as observations have shown that the paralysis of one vocal cord is not a source of danger to the patient. It was first thought, when the operation was performed under local anesthesia, that the voice test would be satisfactory in revealing a cord paralysis but this was proved not to be the case. By the observance of these precautions unilateral paralysis of the recurrent laryngeal nerve occurred in only 12 of 85 consecutive operations.<sup>20,21</sup> In 9 the paralysis was temporary and was followed by complete recovery. Two patients who showed unilateral nerve injury by direct laryngoscopy and in whom the operation was, therefore, terminated, recovered from their paralysis and the thyroidectomy was successfully completed by a second stage operation at a later date.

Inasmuch as every vestige of the thyroid gland must be removed to prevent regeneration and restoration of normal basal metabolism, it is necessary for the surgeon to remember that the pyramidal lobe is found in 35% of patients. This must be searched for and dissected out with great care from between the trachea and esophagus.

This review is not the place to discuss the details of surgical technique, and the reader is referred to Berlin's<sup>19</sup> original description as well as to the preceding papers.<sup>16,17</sup> Surgeons should not undertake this operation without the precautions of familiarizing themselves with the experiences of others and without at least a few practice operations upon the cadaver. While the necessity for painstaking dissection renders the operation rather time consuming, the fact that the thyroid gland is normal renders its removal not particularly hazardous *per se* if the patient has been adequately prepared. The 6 operative deaths previously mentioned were the only ones in a consecutive series of 75 patients, giving an operative mortality of 8%. With the modifications, some of which have just been presented, there have been no operative deaths in the last consecutive 30 cases.

**Preservation of the Parathyroids.** Owing to the necessity for the complete removal of the thyroid gland in this procedure, the danger of damage to the parathyroid glandules or their accidental removal is much greater than in the common operation of subtotal thyroidectomy. Dissections upon the cadaver were carried out by Berlin<sup>20</sup> in order to

be familiar with the various locations in which these bodies were to be found and in order better to recognize them in the course of operation. In 66% of a series of 60 patients, the parathyroids were found to lie just above the lower poles of the thyroid gland where they were in close relation to the end branch of the inferior thyroid artery; 22% lay on the posteromedial aspect of the thyroid close to the junction of the middle and upper third of the adjacent lobe. They were found to lie scattered in various locations in the remaining 12%. Berlin<sup>19</sup> describes the parathyroids as yellowish-brown, flattened oval bodies about the size of a split pea and having a finely granular surface, an appearance especially useful in helping to distinguish them from lobules of fat and from the brownish-red coarse fragments of accessory thyroid tissue. The number of parathyroids present is variable and it is often difficult to demonstrate more than 2 or 3 of them during operation. The inferior ones are observed to be placed more laterally and are often supplied by a long arterial twig, hence their recognition and preservation is seldom difficult.

Armed with much of this knowledge before beginning the surgical removal of the entire thyroid gland, Berlin was able to carry out the operation on 75 consecutive patients in only 14 of whom was there any subsequent evidence of parathyroid deficiency. In all of these 14, the deficiency was controlled either without medication or by the use of calcium alone for comparatively short periods of time. In only 2 instances has it been necessary to continue the administration of calcium and in these the mild symptoms of hypoparathyroidism were completely controlled. It seems evident from these facts that the symptoms observed in these 14 patients were due not to the accidental removal of the parathyroid glands but rather to temporary impairment of their functions as a result of transient interference with their blood, lymphatic or nerve supply. During the course of the 75 operations, 6 parathyroid glands were removed accidentally but in every instance the removed gland was reimplanted in the sternomastoid muscle. The care exercised to identify these glands during operation was attested by the fact that examination of the thyroid glands after removal revealed only two parathyroids.

**Changes Produced by Total Thyroidectomy.** *Their Mechanisms; Clinical Measurements.* Marked reduction in the level of basal metabolism was a constant result of total thyroidectomy. The metabolic rate probably begins to fall quite shortly after the operation, but it requires from 3 to 4 weeks for it to reach a level about 20% below that present before the operation. It is not until such a level has been attained that lasting beneficial results are to be expected,<sup>16</sup> although some relief of symptoms is observed frequently before this has been accomplished. It has been shown<sup>5</sup> that there is a close relationship between the observed improvement of the patient's circulatory state and the extent of fall in his metabolic rate. The metabolic level continues to fall and may reach to well below -40%.

The symptoms and signs of myxedema appear at levels below about -30%, and increase in severity more or less in proportion as the level falls below this point. The unpleasant and possibly harmful symptoms of myxedema can be controlled more or less completely by the administration of thyroid. The dose required seems to lie between 8 and 32 mg.

(gr.  $\frac{1}{8}$  and  $\frac{1}{2}$ ). Too large doses defeat the primary purposes of the thyroidectomy and may induce the return of cardiac symptoms, both those of failure and those of angina. The optimum level for the maintenance of the metabolic rate appears to lie at about -25%, varying slightly in different patients and determinable only by trial under close observation.

It has already been mentioned that Blumgart and his colleagues<sup>5</sup> had found a retarded rate of blood flow in cardiac patients who were suffering from congestive failure. Such patients were also observed to show an increase in the rate of blood flow when their symptoms of failure were relieved by medical treatment. Studies of the velocity of blood flow following total thyroidectomy in a group of patients previously suffering from congestive heart failure showed that the velocity of flow remained slowed, yet these patients were largely or completely relieved of their previously intractable heart failure. The mechanism underlying the relief of failure must therefore have been that of the reduction of the metabolism of the tissues, including the heart, to a level at which the diminished velocity of blood flow was adequate to meet most or all of the tissue requirements. In other words, while the heart is not able to accomplish increased work as a result of thyroidectomy, the reduction in the tissue demands by virtue of the lowered metabolic rate may be sufficient to restore the balance between the heart's capacity and the work (blood flow) required. In some instances it was shown that the work demanded of the heart had been reduced by the lowered metabolism to a level below that of the heart's capacity. In such patients actual cardiac reserve had been reestablished to a limited degree by the thyroidectomy.

Exercise tolerance tests applied under standardized conditions before operation were repeated at various intervals after operation, and their results confirmed both the clinical impressions that the patients had been largely relieved of congestive failure and the belief that the demands upon the heart had been diminished and its reserve increased. Significant improvement in the response to this test was observed even when the patient was retested only a few days after getting out of bed, and before his muscular tone could have been raised by increased physical activity. At this early date the basal metabolism had shown only a moderate degree of reduction, and as it fell to lower levels the patient's circulatory response to the exercise test was seen to improve, sometimes to a remarkable extent. With this measureable improvement in tolerance for exercise the patients observed less and less fatigue, diminished dyspnea, and other subjective manifestations of a restoration of cardiac compensation.

Diminished vital capacity of the lungs is a nearly constant concomitant of congestive failure.<sup>22,23</sup> Similarly, Blumgart<sup>24</sup> and associates have shown that the vital capacity is much lowered in the presence of the lowered metabolism of spontaneous myxedema although such patients were free from congestive heart failure. When, therefore, the vital capacity following total thyroidectomy was found to be increased in some patients and unchanged in others, both groups being similarly relieved of their previous respiratory symptoms, the divergence was readily explained. On the one hand the relief of heart failure tended to restore a greatly reduced vital capacity to normal, on the other the

fall in metabolic rate responsible for the relief of failure tended to reduce the vital capacity. The change which actually may be found in any given patient must, therefore, be the resultant of these two opposed influences.

The blood pressure in congestive failure was not significantly or constantly influenced by total thyroidectomy. Alterations in the electrocardiographic findings were frequent and quite in line with the alterations previously observed in spontaneous myxedema.<sup>25</sup> The outstanding changes were those of lowered voltage of the *Q-R-S* complexes and less frequently lowering in the amplitude of the *T*-waves, or their flattening. Ectopic premature beats were observed to disappear in several patients. They returned in one when the basal metabolism was raised by the administration of thyroid, and again disappeared upon its discontinuance.

One of the most striking alterations observed by the patients has been the frequent, prompt and complete relief of the pains and aches in the chest which often accompany congestive heart failure. These diminished and then disappeared in proportion to the fall in the basal metabolic rate. Recurrent hemoptysis was also relieved in several patients. Despite the relief of the signs of congestive failure and the marked effects upon recurrent hemoptysis, total thyroidectomy has not been followed by encouraging or consistent results so far as the control of paroxysmal dyspnea is concerned. The explanation of this failure is not clear.

Patients with the anginal type of cardiac failure seemingly are more constantly and more greatly benefited by total thyroidectomy than are those manifesting congestive heart failure. A group of such patients has been subjected to a series of carefully controlled observations prior to total thyroidectomy and at various times subsequent to that operation. It was observed that the relief of anginal pain in a number of patients followed immediately after the operation. In this group the relief was evidently not attributable to alterations in the thyroid function and in basal metabolism as these require from 3 to 4 weeks for their development. The mechanism of this early relief of anginal pain was investigated by Weinstein and his associates<sup>26</sup> who found that the pain and the hyperesthesia and hyperalgesia of the chest might all be relieved within as little as 2 hours following completion of the operation. They concluded that these immediate effects could be explained only on the basis of the severance during the operation of afferent nerve paths from the heart. That it was not due to the functional blocking of these paths as a result of local anesthesia or of their depression from trauma or postoperative inflammatory reactions was evident from the fact that the relief persisted. The explanation was further confirmed by demonstration of similar but strictly unilateral relief obtained in anginal patients subjected to hemithyroidectomy. The degree of relief thus obtained was pronounced and sometimes complete, as confirmed by the results of the comparative study of the response to a standardized exercise tolerance test repeated under controlled conditions. The relief was found to be essentially identical with that following cervical sympathectomy and paravertebral alcohol injections. In patients subjected to hemithyroidectomy the pain tended to reappear after periods of from 3 to 6 weeks.

Patients subjected to total thyroidectomy frequently showed both

immediate and permanent complete relief of all anginal pain and hyperalgesia of the chest. In such patients, however, a second mechanism of the relief of pain was introduced. This was brought about by the lowering of basal metabolism and the restoration of the normal relationships between heart work and blood flow. As previously pointed out, this mechanism generally begins to come into play after 3 to 4 weeks following thyroidectomy. In the patients studied, this mechanism was found generally to overlap that responsible for the immediate control of pain so that there was no subsequent recurrence of pain even when the standardized exercise tests were repeated, the amount of effort being markedly increased.

Further studies by Eppinger and Levine<sup>27</sup> showed that the response to the injection of adrenalin<sup>28</sup> was either greatly diminished or completely abolished immediately after thyroidectomy, thus adding confirmation to the observations of Weinstein and his associates.

Shambaugh and Cutler<sup>29</sup> carried out experimental studies on dogs in which they endeavored to test the effects of total thyroidectomy upon the production of pain by coronary constriction according to the method of Sutton and Leuth.<sup>30</sup> They found that thyroidectomy did not alter the pain response caused by this mechanical interference to coronary blood flow and they suggest that the beneficial effects of total thyroidectomy in man may be attributable to an interference with the thyroidal mechanism. They believe this to be especially likely as the explanation in view of the observations of Levine and his associates<sup>28</sup> just cited.

#### Miscellaneous and Collateral Studies Following Total Thyroidectomy.

The development of myxedema was an expected consequence of total thyroidectomy. That myxedema may, itself, lead to cardiac enlargement, loss of heart efficiency, and even to congestive heart failure has been pointed out by Zondek,<sup>31</sup> Fahr,<sup>32</sup> Tung<sup>33</sup> and others.<sup>25</sup> The true "Myxedema Heart" appears to be relatively infrequent and signs of congestive heart failure as a result thereof are apparently rare.<sup>34,35</sup> Cardiac enlargement, diminished excursion of the chambers as seen fluoroscopically, and lowered potential of the Q-R-S and T waves of the electrocardiogram occur not infrequently. Their precise mechanisms of production remain debatable.

Davis<sup>36</sup> and his associates, therefore, studied the effects upon the heart in 37 patients upon whom total thyroidectomy had been performed. Symptoms and signs of myxedema developed after periods of 3 to 8 weeks following thyroidectomy and were readily controlled by small doses of thyroid extract. In a group of 22 patients operated upon for the relief of congestive heart failure the development of myxedema was accompanied by some enlargement of the heart teleoroentgenogram in 15; there was no change in 3 and slight decrease in size in 4 patients. The largest increase in size amounted to 2.7 cm. in the total transverse diameter, the greatest decrease to 1.4 cm. Among 11 patients with previous angina pectoris, 8 showed similar increases and 3 showed no change in transverse cardiac diameter. The changes in heart size were studied in relation to the progress and extent of the hypothyroidism on the one hand, and on the other to the alterations in signs and symptoms of heart failure. It was found that in the angina cases the alterations in heart size and in electrocardiographic voltage



ran parallel to the degree of the hypothyroid state. In the group which had previously had congestive failure there was no such relationship, the alteration in the size of the heart being the result of two opposing factors: diminution in heart size resulting from relief of congestive failure and enlargement of the heart due to myxedema. If the level of basal metabolism be kept at about  $-30\%$  there seems to be little or no tendency for the signs or symptoms of hypothyroidism to progress.

In view of the established relationship between the level of thyroid activity in thyrotoxicosis and spontaneous myxedema and the level of the blood cholesterol content, studies were carried out to determine this relationship in the group of patients subjected to total thyroidectomy.<sup>37</sup> The results showed that the level of cholesterol rises as the basal metabolic rate falls and parallels more or less closely the appearance of clinical signs of hypothyroidism. Such changes begin to become appreciable within about a week after operation and are marked by the end of the first month. Although the basal metabolism does not fall significantly after the first month or 6 weeks, the cholesterol level continues to rise along with progression in the clinical signs of hypothyroidism. Clinical symptoms of hypothyroidism usually appear at blood cholesterol levels of about 300 mg. per 100 cc. and a basal metabolism rate of  $-30\%$ . The administration of small doses of thyroid extract not only causes an elevation in the depressed level of basal metabolism but diminishes the cholesterol content in the blood.

Means and Lerman<sup>38</sup> point out from their prolonged clinical observations that patients with spontaneous myxedema may be maintained in excellent health for many years by the appropriate use of thyroid extract. Such patients have naturally a more even level, though greatly depressed, of basal metabolism than do normal patients and it is possible in such patients so to gauge the administration of thyroid as to control both the symptoms of myxedema and to maintain almost any desired level of basal metabolism. Between the levels of  $-20$  and  $-30$  such patients show generally but slight symptoms while, if the metabolic rate be elevated to about  $+10$ , symptoms of hyperthyroidism may make their appearance. A daily dose of 32 mg. ( $\frac{1}{2}$  grain) of thyroid will maintain the basal metabolic rate at about  $-20$  in the average myxedematous patient. Their studies also showed that a long period of time is required for the development of cachexia.

In the present series of patients with artificial myxedema there has been to date no evidence of development of progressive arteriosclerosis. Similarly, while many patients have shown a slight fall in both the numbers of red cells and the hemoglobin percentage, such changes have not been progressive nor have they resulted in symptoms which have required the administration of iron for the control of the anemia.

The metabolism of sugar was investigated in a group of these patients by Gilligan<sup>39</sup> who found it to be essentially uninfluenced as a result of the induction of hypothyroidism in patients whose pre-operative sugar metabolism had been normal. The production of hypothyroidism in a diabetic patient and in a patient who had hyperthyroidism resulted in marked decreases in hyperglycemia produced by the ingestion of glucose. Extending this study, Abrams and Gilligan<sup>40</sup> found that in non-hyperthyroid and non-diabetic patients the development of hypothyroidism following operation was without influence upon their

response to the injection of 20 units of insulin. Furthermore, the evidences of mild hyperinsulinism occurred at the same levels of blood sugar both before and after the development of hyperthyroidism. They conclude that the response of the sympathico-adrenal system is normal in these patients and that no antagonism exists between the internal secretion of the normal thyroid gland and the pancreas.

**Hypoparathyroidism.** Among 73 consecutive patients upon whom total thyroidectomy had been performed none showed either spontaneous spasm in the extremities or tetanic convulsions.<sup>41</sup> Twelve (17%) showed slight signs of mild hypoparathyroidism in 10 of whom these were transient, lasting for less than 2 weeks. The symptoms were limited to various degrees of paresthesia, to the appearance of Chvostek's and Trousseau's signs and slight but inconstant diminution in the level of serum calcium without consistent or frequent rise in inorganic serum phosphorus. The administration of calcium chlorid and an abundance of milk generally controlled the symptoms promptly. Calcium lactate or gluconate was used where the patient did not tolerate calcium chlorid. In the 2 patients who showed a persistent mild hypoparathyroidism, the symptoms could be controlled successfully by the combination of viosterol with a high calcium intake.\*

**Summary of Results.** *Present Criteria for the Selection of Patients; Additional Incidental Observations.* Blumgart and his associates<sup>42</sup> have analyzed the results of total thyroidectomy performed on a group of 75 patients suffering from chronic heart disease without clinical evidence of thyrotoxicosis and in whom the ablated thyroid glands were proved, upon examination, to have been normal. All of the patients had been long incapacitated despite all efforts at relief by recognized therapeutic measures. Fifty of the patients suffered from chronic recurrent congestive failure. In 29 of these the failure was due to rheumatic heart disease and in 17 to arteriosclerotic heart disease with or without hypertension. There were 2 cases with congenital heart disease and 1 each of syphilitic heart disease and cor pulmonale. The ages ranged between 18 and 69 years. The sexes were equally represented.

The degree of clinical improvement produced by the operation was judged by changes in the usual clinical signs of congestive failure such as pulmonary congestion, orthopnea, edema, cyanosis and the like as well as by the patient's responses to various functional tests. Twenty-four have maintained compensation sufficiently to be able to work for periods varying from 2 to 18 months. In 6 congestive failure recurred temporarily but responded to the usual methods of treatment. There were 6 operative deaths and 6 deaths occurred at periods too late to be attributable directly to the operation. Two patients were not benefited by the operation. Of the compensated cases, 8 have maintained their compensation for periods of a year or more. Among those showing recurrent failure the cause could not be determined in 3. The recurrence was due to overactivity in 1; to the reappearance of bronchial asthma and to the discontinuance of digitalis in 1 each. Among those who died

\* [Note: I have been observing one of these patients who, after nearly 18 months remains on the borderline of hypoparathyroidism which necessitates his receiving a high calcium intake and a small daily dose of parathyroid extract, without which he promptly approaches having tetany.—EDITOR.]

between 3 weeks and a year postoperative, death was due to cardiac failure in 3; to cerebral embolus and pulmonary edema in 1 each and to unknown causes in the sixth. Of 32 patients with angina pectoris who were operated upon, in 19 angina was the major disabling factor. In 5 of the remainder cardiac asthma was of first importance and in 8 congestive failure. The anginal syndrome was sufficiently pronounced in 25 of this group to permit the evaluation of the effects of operation. In this controlled group, 8 have shown no recurrence of angina over a period of 3 to 18 months in spite of marked physical activity.\* Five previously completely incapacitated have had only occasional attacks since operation and their range of activity has been markedly increased so that they could return to some form of occupation. In 2 patients anginal attacks have recurred after a period of complete relief in the one following an accident, in the other, a coronary occlusion. Marked increase in the level of metabolic rate produced by thyroid administration caused recurrence of angina in 3. One patient in the anginal group died following coronary occlusion 3 months after operation after a period of complete relief from angina. All but 4 showed more or less marked increase in their tolerance to exercise. These 4 have attacks of angina in response to exercise which have been quite uninfluenced by operation and have been unable to resume any form of work. Three of these 4 unsuccessful cases were patients having low preoperative basal metabolic rates ranging between  $-19$  and  $-24\%$ .

Experience to date indicates that the best results from total thyroidectomy are to be obtained in those patients with chronic congestive failure due either to rheumatic or hypertensive arteriosclerotic processes who can be restored to compensation when at rest in bed. Those who do not respond to rest in bed in conjunction with the customary methods of medical treatment, on the other hand, are likely to derive relatively little benefit from the operation and are also such poor surgical risks as to make the operation too hazardous. Since the basic theory underlying this method of treatment rests upon a restoration of the normal balance between the heart work and basal metabolism, the choice of patients should for the most part be limited to those whose pre-operative metabolic rate is not more than about  $15\%$  below normal standard. Experience has shown that patients falling below this level show very little benefit. Similarly in the case of the anginal group of patients those with significantly depressed basal metabolism show little improvement and the best results are obtained among patients whose attacks of angina occur upon very mild exertion but not when the patient is

\* [One of these patients has been studied recently in our clinic. He was operated upon in November, 1933, with complete relief for several months and a great increase in his exercise tolerance without the induction of angina. For many months past he has, however, suffered greatly from the discomforts of his myxedema at a metabolic level of about  $-25\%$ . If his dose of thyroid is increased and his metabolism thereby elevated just enough to make his myxedema bearable he suffers from his angina about as severely as before operation. Even with a  $-23\%$  level of metabolism he has angina on cool days, on climbing slight grades, and has been quite unable to work. Tested on the standard steps in a warm room anginal pain now returns after the same amount of effort which was required just prior to operation. The patient stated that if he had known in advance what the discomforts of moderate myxedema were, he doubts if he would have undergone thyroidectomy. In his case it is practically impossible to adjust the administration of thyroid so that both his angina and his myxedema are bearable.—EDITOR.]

at rest. If a sufficient period of time be allowed to elapse following its occurrence the previous development of coronary occlusion is not a contraindication to thyroidectomy. No patient should be operated upon who shows evidences of active infection, recent vascular accident, pronounced renal disease or the evidence of active rheumatic disease.

Certain changes have come about in the pre-operative preparation of patients in addition to those already cited. Not only should every effort be made to restore compensation but in patients suffering from auricular fibrillation, it seems advisable to use rather larger doses of digitalis than otherwise just before operation so as to make sure of controlling ventricular rate. Whatever sedatives may be needed should be well tried out during the pre-operative period of study to determine the patient's reaction and to exclude the presence of idiosyncrasy. As little sedative as possible should be used during the operative period. The employment of oxygen therapy may diminish operative results in a certain proportion of cases.

*Postoperative Medical Management.* Except for the necessity of regulating the level of hypothyroidism, there is generally very little medical care required following operation in patients with angina pectoris.<sup>43</sup> Many of these patients may be allowed to be up as shortly as 48 hours after operation and may even be discharged from the hospital within a week to 10 days. It is, however, better to retain such patients under hospital control sufficiently long to see them through their adjustment periods and if possible to establish appropriate control of their metabolic level by thyroid administration.

Patients operated upon for the relief of chronic congestive heart failure generally require more prolonged postoperative convalescent care. Where compensation can be restored completely before operation, the period of postoperative convalescence rarely needs to exceed 3 weeks but the usual regimen for the control of chronic heart failure should be continued. There should be a gradual adjustment in the amount of physical effort permitted. The administration of digitalis should be continued in doses appropriate to the needs of the individual patient. This is especially important during the first 4 to 6 weeks, the period before hypothyroidism becomes well established. In all cases, but especially in those with previous congestive failure, the resumption of physical activity as well as the degree of activity allowed should be gradual and should be permitted only under close supervision. In this group with previous congestive failure, Mixter, Blumgart and Berlin<sup>16</sup> recommend that the patient be kept for the most part at rest in bed until basal metabolism has fallen to at least -20% in order to protect the patient against the recurrence of congestive failure from the too prompt resumption of activity. The management of the cardiac condition in such patients is generally the same after operation as before so far as drugs are concerned and it is commonly necessary for such patients to continue the use of digitalis especially those showing auricular fibrillation.

**Comment.** The introduction of a new therapeutic agent or procedure, especially when its results appear dramatic, is likely to be received with excessive and often unwise enthusiasm. The critically scientific attitude of the proponents of total thyroidectomy, together with their manifold precautions in the selection and care of otherwise seemingly

hopeless cases so imbues all of their papers with conservatism that an excess of unbridled enthusiasm may have been prevented. If this be true, then the lapse of time should permit that controlled study of total thyroidectomy which must be undertaken on a purely experimental basis before it can be safely accepted, rejected or admitted into rational therapeutics on a narrowly yet soundly restricted basis. It is certainly not yet the time to attempt conclusions as to its true place as a remedial measure. Much more knowledge concerning all of its results must be accumulated before that can be done. At present it should continue to be regarded as an experiment of some promise.

Among the many problems raised, the following seem of most immediate importance. Are the results in cases of congestive failure enough better than those of the best medical treatment<sup>44,45</sup> to justify either the risks involved, or the very considerable handicaps and discomforts of myxedema? What proportion of patients with congestive failure cannot be maintained in a reasonably satisfactory condition by the best possible medical treatment? It would appear to be extremely small if those be excluded in whom the heart lesions are inevitably progressive. If thyroidectomy is of real benefit in this small group, can we develop still better and more accurate methods for their recognition? Is there any evidence to suggest that the progress of the underlying disease of the heart or arteries is altered by thyroidectomy? Does artificial myxedema induce vascular changes like those found in the spontaneous disease, or does it promote the advance of such changes as may already be present? In what percentage of patients can thyroidectomy be anticipated to maintain cardiac compensation for more than one year? Is the duration of reasonably comfortable life materially prolonged?

The results of thyroidectomy appear to be somewhat better and more likely to be secured in patients with angina and in those with cardiac asthma than in other types. In some the results have been truly dramatic. Can we improve our present methods for selecting patients who will fall in this latter group? Many of the problems are the same for the anginal cases as for those with congestive failure and do not need repetition. It remains to be determined what percentage of anginal patients will be relieved for as long as one year. It is not always possible to control the sufferings of myxedema without reinducing angina. In what proportion of patients is such an adjustment feasible? Is the comfortable life of the anginal patient significantly prolonged? Is life expectancy lengthened?

Space prevents further comment along these lines, but it must be pointed out that cardiac failure occurs spontaneously in persons with low basal metabolism and even in the presence of spontaneous myxedema. It seems justifiable, therefore, to raise the question: Is total thyroidectomy a procedure of more than temporary value?

Whatever the ultimate status of total ablation of the normal thyroid gland may be proved to be, its proponents deserve high praise for the theoretical soundness of their conceptions, their originality, their caution and their courage.

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(Titles have been omitted for sake of brevity.)

## RADIOLOGY

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## RADIOTHERAPY.

THE specific sensitiveness of each kind of cell looms up as the dominant single fact in radiology, and, Desjardins<sup>1</sup> asserts, if reaction time is taken as a criterion, deserves to be recognized as a law. The sensitiveness peculiar to each kind of cell appears to be related chiefly to the natural life cycle. Thus the lymphocytes, the metabolic cycle of which among human cells is the shortest, are the most radiosensitive, while the nerve cells, the life cycle of which is the longest, are the most resistant to irradiation. The notion that pathologic cells are more radiosensitive than normal cells of the same kind is valid only to the extent that the rate of mitosis of cells is affected by the pathologic disturbance. The significance of this factor, therefore, is limited to tumors and to processes of which cellular hyperplasia is an important feature. Such influence is small as compared with the specific natural susceptibility of each variety of cell and with the age or metabolic status of the cells. Cellular radiosensitiveness, therefore, is the natural reactivity of different kinds of cells to a given quantity of radiation of a certain quality (average wave length) when the cells are exposed in a certain way (scheme of irradiation) as estimated clinically by an experienced radiologist. Radiosensitive tumors are growths the sensitiveness of which is greater than that of the skin; moderately radiosensitive tumors have a sensitiveness approximating that of the skin, and radioresistant tumors one less than that of the skin. Certain factors are known to cause variations in the radiosensitiveness of neoplasms, among them may be mentioned impairment of blood supply, disturbance in anatomic relations, acting mainly by interfering with the circulation and lymphatic drainage and by inducing the formation of connective tissue, cachexia by reduction of the patient's resistance, sepsis, the influence of which is not understood, and previous irradiation. Lessened radiosensitiveness from previous irradiation probably results from the gradual secondary proliferation of connective tissue which follows the destruction of malignant cells, as well as from the increasing inhibition of mitotic activity of the malignant cells from repeated irradiation and also from diminishing blood supply. Numerous attempts to increase the sensitiveness of tumors have been made by injecting intravenously various dyes and other substances, but the results have not been sufficiently striking and conclusive to command wide acceptance. Desensitization of the skin by reducing the circulation through the cutaneous vessels by pressure during the time of irradiation has not been conspicuously successful.

Landauer,<sup>2</sup> in reviewing the physical aspects of various qualities of radiation, feels that only that radiation which is absorbed produces any biological reaction. The greater the quantity of radiation absorbed, the greater will be the beneficial effect. The harder the radiation, the greater the quantity absorbed as it is measured from depth dose measurements. Craver and MacComb,<sup>3</sup> reviewing their experience with the Heublein method of continuous irradiation at low intensity, over periods of several days to 3 weeks, of the entire body, with target-skin distance of over 5 meters, consider it a valuable addition to the treatment of several radiosensitive tumor processes, such as leukemias, lymphosarcoma, Hodgkin's disease and multiple myeloma, and that its results in the treatment of chronic lymphatic leukemia and pseudoleukemia are superior to those obtainable by local irradiation. They found it to be of only slight value in the treatment of radioresistant tumors.

Elliott and Jenkinson<sup>4</sup> report a case of ulcerations of the stomach and small intestine following Roentgen therapy, with perforation and death. Kaplan<sup>5</sup> very comprehensively reviews the problem of the care and treatment of chronic cancer cases. He groups these as (1) those for whom something radical can be done in the form of intensive treatment, and (2) those for whom only such measures can be undertaken as will relieve mechanical or functional disturbances of normal body condition. The chronic cases are divided into those which may be treated (a) as ambulatory cases in the routine follow-up clinic, (b) in the home, and (c) in the hospital.

Eller<sup>6</sup> asserts that the therapeutic potency of Roentgen rays is well established and leads the field of dermatological physical therapy. In some cases, such as mycotic infections (ringworm and favus) of the scalp, keloidal formations and hyperidrosis, Roentgen rays alone can improve the condition. In other conditions, such as plantar warts, beard infections and epitheliomas, this method of therapy is most valuable. In psoriasis, eczema, lichen planus, ringworm of the glabrous skin, certain epitheliomas, etc., Roentgen rays are used in combination with other medical and surgical procedures with advantage. Radium, even though it is not used as extensively as Roentgen rays, is often a great aid to the dermatologist. It has a distinct advantage in the treatment of certain lesions, such as epitheliomas or keratoses located near the inner canthus of the eye or alæ of the nose. Also radium gives by far the best cosmetic results in angiomas and certain other vascular nevi.

Grenz rays are Roentgen rays of extremely long wave length (8 to 10 kv.) and are useful in: multiple flat epitheliomas of the skin; verrucæ planæ of the bearded region or other areas of the skin; localized neurodermatitis; eczematous conditions of the scalp, eyebrows and eyelids; certain cases of dermatophytosis of the glabrous skin; sarcoids; and superficial lesions of lupus vulgaris. Roentgen rays are used in dermatology for the following: Conditions in which it is desirable to epilate hair temporarily, such as tinea capitis, favus, sycosis and nevus pilosus; to reduce the activity of the sebaceous glands, as in acne vulgaris, acne rosacea and seborrhea; to inhibit the function of the sweat glands, as in hyperidrosis, bromidrosis, chromidrosis, pompholyx and hydrocystoma; to change the metabolism of the regional cells or produce an environment that is less favorable for the growth and reproduction of bacteria and fungi, as in skin tuberculosis, sycosis vulgaris, fungus infec-



tions, selected cases of furunculosis, acne varioliformis, etc.; and for the relief of pruritus. Most superficial therapy is done with unfiltered radiation. Only a few dermatoses are treated by filtered Roentgen rays. In sufficient doses, soft Roentgen rays can produce a caustic and destructive effect. The dosage of Roentgen rays has been based upon the skin unit, *i. e.*, the dose required to produce a temporary epilation of the hair of the scalp. Translated into roentgens, one skin unit is equivalent to about 350 r. Variations in susceptibility to irradiation play an important part in the production of sequelæ. Telangiectasæ subsequent to irradiation usually occur within 2 years, although they may not appear until the third, fourth or even the fifth year.

In radiation therapy of cancer of the skin, Grier<sup>7</sup> advises irradiation as the treatment of choice; unfiltered radiation is preferable, and massive doses produce the best results in his experience. Seven times an erythema dose is the minimum that should be used. He bases dosage on the physical characteristics and the history of the lesion rather than upon microscopic findings. An analysis of his own cases convinces him that the most common cause of failure or recurrence is underdosage. In the treatment of psoriasis in Bellevue Hospital, Rosh<sup>8</sup> has used Roentgen irradiation of the sympathetic nervous system, which at the same time affects the thymus tissue. The application of high voltage Roentgen rays to the spine at those levels which correspond with the nerve supply to the affected parts first increased the itching, but this was soon followed by complete cessation of this symptom. After 3 weeks' treatment the color faded from the center of the affected areas, the scales became loosened, and the surrounding infiltration in the skin was diminished. In most cases a second series of treatments was given after a period of 6 to 8 weeks, during which time a majority of the areas were replaced by a brownish pigmentation. Complete disappearance of the lesions occurred in 3 to 6 weeks after the administration of the last treatment. In some persistent cases, a year elapsed before the body was free from psoriasis.

In the treatment of acne vulgaris with Roentgen rays, MacKee and Ball<sup>9</sup> reported 60% of their patients clinically cured with one course of treatment, *i. e.*, in 4 months or less. Recurrences totaled approximately 11%. Without Roentgen ray treatment there were approximately 40% failures; with Roentgen ray treatment the failures amounted to about 5%. In their experience, radiotherapy offers the most certain method of obtaining a clinical, and even a permanent cure, in the shortest time. Morrow and Taussig<sup>10</sup> discuss radium dosage and technique in benign lesions of the skin. In their experience there are but few conditions responding to radiation in which the Roentgen ray is not at least equal to radium. Radium is generally considered superior, or at least equal, to the Roentgen ray and other forms of therapy in vascular nevi, nevus flammeus (port-wine mark), nevus vasculosus (strawberry mark), cavernous hemangiomas and fleshy nevi; none of these should be treated by Roentgen therapy. Roentgen radiation is usually preferred in keloids. Roentgen rays and radium are equally efficacious in the treatment of verrucæ; the same applies in synovial cysts, and radium is preferable for epulis in the vascular type occurring between the teeth; the other types are most satisfactorily treated by electrothermic surgical methods. The greatest danger in the use of radium in the therapy

of dermatologic conditions is that of late sequelæ; telangiectases, atrophy, keratoses, and even malignancy.

Pfahler and Vastine<sup>11</sup> state that if all the knowledge that is now available is utilized skillfully, practically all cancers of the skin can be prevented and, if they occur, and are treated reasonably early while the disease involves only the skin, they should be cured. They stress the treatment of precancerous lesions; moles, particularly the pigmented moles, should be removed; likewise, all warts and particularly senile warts, any abnormal crusts, fissures or chronic ulcers. The fear of operation often keeps a patient from coming to a physician; radiotherapy eliminates this fear, and radium, Roentgen rays, electrocoagulation or surgery, separate or combined, may be discussed later with the patient, as the individual case suggests.

The rate of recuperation of human skin following irradiation was studied by Duffy *et al.*,<sup>12</sup> and they considered the skin to be an obvious indicator of the degree of damage produced and the rate of recovery in tissues an important factor in all methods of irradiation. Dividing the procedures into the three fundamental types: massive, fractional and saturation dosage, *i. e.*, where the maximum effect is obtained through a single exposure to radiation (massive); where the maximum effects are obtained by the gradual administration of small doses (fractional); or the maintenance for a certain time of a biologic effect already present, by the addition of smaller doses (saturation). Using the gradual fading of the reaction after treatment as an evidence of recuperation of tissues from radiation damage, they determined the quantity of radiation necessary to produce equal skin reactions in single and divided doses of 200 kv. Roentgen rays filtered by 0.5 mm. of copper and 2 mm. of aluminum, using the threshold erythema as a standard reaction for comparison. The threshold erythema dose for a single exposure was 525 Roentgens; for equal amounts given at intervals of 24 hours, 400 Roentgens for each exposure and, for equal amounts given at intervals of 48 hours, 425 Roentgens for each exposure. They found the skin recovered 69% of the immediate damage in 24 hours and 76% in 48 hours.

Howes<sup>13</sup> presents a group of cases of all types of epitheliomas of the skin and lip treated by one massive dose or divided doses on consecutive days, and considers his results comparable with other accepted forms of treatment. Widmann<sup>14</sup> comments that the popularity of irradiation procedures for carcinoma of the lip has become international, and attributes this to the relative simplicity of administration, as well as the speed and economy with which result is obtained. There is practically no treatment mortality, no risk of hemorrhage or infection, and the cosmetic results are excellent. His best results were obtained in small lesions and with adequate treatment of lesions of short duration. He found no evidence to indicate that irradiation will consistently effect regression of metastatic nodes. Surgical excision seemed justified of isolated, freely movable nodes that develop after apparently adequate high voltage Roentgen ray or radium pack treatment. Prophylactic irradiation of the cervical node region is warranted by his experience. He favored free and wide electrodesiccation in conjunction with radium or Roentgen rays in small lesions.

Kaplan *et al.*<sup>5</sup> discuss the protracted external irradiation method in

the treatment of carcinoma of the mouth and throat, and compare their results with Roentgen rays, the 5-gram pack and the small radium pack. Martin and McNattin<sup>15</sup> compare the results in the treatment of cancer of the pharynx, tonsil and extrinsic larynx by divided doses of external radiation with the Pfahler saturation technique, a fractional dose method based largely on the theory that there is a loss of radiation effect at a definite rate and that by daily repetition of a certain percentage of the original dose, this loss is replaced so that the original effect is maintained or prolonged for a desired period; and that of Coutard, which is based on the theory that the effect of multiple daily doses of external irradiation is cumulative, and that there should be a steadily increasing radiation effect brought to a climax after 2 to 4 weeks of treatment. The total doses employed by Coutard are much larger than those given by any other method of external irradiation. Such intense biologic effects as a blistering or epidermicidal reaction of the skin and a membranous mucositis in the pharynx are deliberately produced as a requisite to the accomplishment of a lethal effect on the underlying tumor. Coutard demonstrated that these biologic effects on the skin and mucous membrane invariably healed without difficulty. By such repetition of daily doses there is a greater differential effect as between normal and neoplastic tissue than if one or only a few massive doses are given at longer intervals. They feel the divided dose technique for the treatment of pharyngeal cancer, or cancer in general, has not been as widely emphasized as its merits deserve. The technique of the Coutard method is given in detail. Lenz *et al.*<sup>16</sup> review a series of cases of epithelioma of the pharynx and larynx treated by a modification of the Coutard method. Pfahler<sup>17</sup> has tabulated his results in the treatment of cancer of the mouth by surface and interstitial irradiation. His custom is to begin with radium packs or high voltage Roentgen rays externally to control at the beginning the spread of the disease. This is followed almost immediately by local surface applications of radium inside the mouth, usually alternating the local application one day with an external application the next, so that the patient does not become too much disturbed by one form of treatment. The applications are made successively on all sides of the tumor area, so that all parts of the tumor tissue shall receive from 6 to 10 erythema doses, counting the external radiation. As director of a state institute founded primarily for the purpose of research concerning the causes and the treatment of cancer and allied diseases, working with a personnel consisting of a surgeon, a radiotherapist, a physicist and a pathologist, supplemented by other specialists interested in cancer therapy, Simpson<sup>18</sup> is convinced that a large percentage of lip and intraoral cancer cases have established metastases which are not demonstrable. The consensus of opinion in his group is that in most cases radiation is the preferable method of treatment for metastatic deposits in the neck. He discusses their results with implantation (gold seeds of radon), external radiation (Roentgen ray) and radium in such cases.

Pfahler and Kapo<sup>19</sup> review the results in the Roentgen treatment of 333 consecutive cases of cervical adenitis. Following a brief review of the anatomy of the lymphatics of this region, they discuss the more common causes of cervical adenitis and the differential diagnosis. They, and their surgical colleagues also, were convinced of the superior value

of Roentgen irradiation in the treatment of cervical adenitis. The treatment can ordinarily be given without hospitalization; the majority can be cured with from 2 to 4 treatments; and with present technique, atrophy and telangiectases can be avoided. Butler and Woolley<sup>20</sup> feel that Roentgen therapy has a definite place in the treatment of chronic paranasal sinusitis in properly selected cases. There is no damage to normal structures when properly applied, and failure of Roentgen ray therapy in no way interferes with subsequent surgical intervention, should this become necessary. Their results were better in cases given single, full doses than in those in which fractional dosage was employed.

Merritt and McPeak<sup>21</sup> reported 6 cases of cystic bone disease which were either entirely cured or definitely benefited by Roentgen therapy applied over the parathyroid region. Fried<sup>22</sup> considers syringomyelia as particularly suitable for Roentgen therapy because the pathologic structure of this disease is highly responsive to the action of the rays. Radiation can halt the inflammatory process in nerve cells and fibers similarly to its action in any other inflammation. In order to obtain the best results it is necessary to commence treatment early in the course of the disease. When the condition has reached the destructive stage, radiation can still interfere with the process and preserve the residual function of the cord which has been retained in the tissue. When no definite improvement takes place by the end of the first series of treatments, a favorable effect can hardly be expected from further irradiation.

Brunschwig and Kandel<sup>23</sup> made studies to correlate the histologic changes and the clinical symptoms in irradiated Hodgkin's disease and lymphoblastoma involving lymph nodes, and to determine, if possible, the reason for the failure of irradiation therapy to eradicate the disease. They concluded that if Hodgkin's disease affected the entire reticuloendothelial system from the start, little more than palliation could be expected from irradiation therapy. If, on the other hand, the process is at first a local one, and if the involved group of lymph nodes is discovered early in the progress of the disease, intense local irradiation, with the object of completely sclerosing the lymph nodes, may offer a possibility of arresting the process. From the histologic standpoint, lymphoblastoma is more radioresistant than Hodgkin's disease. Irradiation of lymphoblastomatous nodes, if the process is of the more malignant type, may result in a reduction of size and some sclerosis; in the chronic cases the nodes are reduced in size, but not sclerosed.

In the discussion of radium dosage and technique in treatment of carcinoma of the breast, Taylor<sup>24</sup> states that the treatment of choice for operable carcinoma of the breast is radical surgery. In the treatment of inoperable and recurrent cases the chief dependence has been upon Roentgen therapy. Radium treatment was essentially palliative, and used as a part of a general plan of radiation therapy, most of which was delivered in the form of Roentgen rays. Following the methods of Geoffrey Keynes, selected cases were treated. Regression of the local process was secured in almost all cases, and seemed to be better than that secured with Roentgen treatment alone. Richards<sup>25</sup> presents a jacket which he devised to solve the difficulty of delivering to the curved surface of the thoracic wall, in the treatment of secondaries in

this region from carcinoma of the breast, a dose of irradiation which would be evenly distributed over the entire area and at the same time effective. The jacket was fitted to the individual patient and provision was made for the attaching of rows of radium needles, accurately spaced from each other, from the midline in front as far as thought advisable. Approximately 100 needles, 60 mm. in length, contain 3 mg. of radium element and having a wall thickness of 0.8 mm. of platinum (standard platinum iridium) were used and left in position from 90 to 100 hours. The reaction which follows is fairly severe, a first to second degree erythema with vesication, and requires very particular care in its treatment.

Baum<sup>26</sup> reports a case and presents a survey of the recent literature on radiation therapy in carcinoma of the bronchus. He includes a study of the end results in the literature of the surgical treatment of this condition, and concludes that irradiation is to be preferred in the treatment of lung carcinoma. Only comparatively early cases are suited for lobectomy; the insidious nature of the disease makes early diagnosis practically impossible; lobectomy carries a high mortality (20 to 30%); radiation by Roentgen ray or radium, or both, has no immediate mortality; and even if life is not prolonged by radiotherapy, the patient's suffering is greatly lessened, and what life remains is made more endurable.

Henry Schmitz<sup>27</sup> reviews a series of 662 cases of carcinoma of the female genitalia treated by irradiation. The number and per cent of the cases involving the vulva, vagina, cervix uteri, corpus uteri and ovaries are tabulated. Eighty per cent of the carcinomas were located in the cervix. The extent of the growth of carcinoma of the uterine cervix decides the rate of curability; the freely movable, clearly localized growths show from 80 to 90% good end results after a 5-year period. So he stresses the careful investigation of chronic cervicitis, low-grade chronic inflammations which frequently precede carcinoma, and follow-up of infections, abortions and lesions resulting from childbirth with adequate treatment of abnormalities to prevent cancer. Silent, early carcinomas found during these examinations, adequately treated, will achieve permanent healing in the majority of cases. Montgomery and Farrell<sup>28</sup> found the hopefulness of prognosis in carcinoma of the ovary was proportional to the grade of malignancy. The histologic findings of 22 cases were correlated with the gross pathologic appearances. The results of postoperative therapy were palliation of symptoms frequently, lessening of pain and recession of edema, with definite prolongation of life in many patients. Simpson<sup>29</sup> presents in detail the technique of treatment of cancer of the cervix with radon. He thinks radon has the advantage of being less bulky than radium, prefers the use of large quantities of radon, such as 1000 mc., for short periods of time to that of small quantities of radium for long periods of time; believes intrauterine treatment should be delayed until treatment against or outside the cervix has rendered it patent; that if the uterine canal has been once invaded, further intrauterine treatment should be delayed for a period of at least 6 weeks, and advises against the current practice of implanting the cervix.

Healy and Arneson<sup>30</sup> combined routine Roentgen irradiation for the distant pelvic involvement and radium for the cervical lesion, giving

the Roentgen ray cycle before application of radium in all but the earliest cases. This has seemed to be advantageous in diminishing the discharge as well as the bleeding, and in reducing the gross size of the primary lesion by causing the superficial, infected and friable tissues to disappear. As a result, there is also less swelling and induration in the surrounding tissues. In this way the cancer field is in much better condition to react satisfactorily to the application of radium, and usually the local and constitutional reactions are less severe. This report deals with an attempt to control parametrial disease by increasing the amount of external irradiation with Roentgen rays so as to obtain a greater intensity of radiation within the pelvic structures without causing severe damage to normal tissues. In the earliest cases radium treatment precedes the Roentgen ray.

The first important advancement in the treatment of carcinoma of the rectum was surgical, and for many years surgical intervention was the only method of treatment. With the advent of radium and Roentgen rays, however, the field of treatment has been extended, and radiotherapy in this field is destined to be of as much value as surgical treatment has been; from a combination of the two methods great benefits will be inevitable. With this introduction, Bowing and Fricke<sup>31</sup> present various tabulations of the situation and classification of rectal tumors, the age incidence, clinical data, index of malignancy, classification of the length of life by grade of malignancy, and a review of the procedures in 500 cases. They believe that therapeutic radiology, especially radium therapy, has a distinct place in the treatment of carcinoma of the rectum, anus and rectosigmoid. Preoperative radium therapy should receive special consideration and, when employed, should be followed by a period sufficiently long, probably 8 to 12 weeks, before surgical intervention is attempted. Radium therapy as a palliative procedure is of value, and inoperable and recurring lesions should be given at least one well planned treatment. The degree of palliation naturally varies, but nearly all the patients will be benefited somewhat. Radium therapy as a postoperative measure has a limited field of usefulness; all lesions of a high grade of malignancy at least should be treated. Roentgen therapy is of value, and with the increased voltage of the present-day installations, should become of greater value, especially in cases in which lesions are of the higher grades of malignancy. These authors, with Counseller,<sup>32</sup> have studied the results of treatment of carcinoma of the penis. Epithelioma of the penis is a slow-growing neoplasm which is inclined to remain superficial for a long time, to metastasize late and, when such metastases do occur, to affect the inguinal nodes. The slow growth and accessibility of the lesion render it amenable to surgical treatment and to irradiation with radium and Roentgen rays alone, or probably best in combination. In inoperable cases, irradiation alone accomplishes a great deal in the way of palliation.

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(Titles have been omitted for sake of brevity.)

## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 18, 1935

**Studies in the Mechanism of Kaolin Hypertension.**—WILLIAM ALLEN JEFFERS, M. AUGUST LINDAUER and JOHN Q. GRIFFITH (Robinette Foundation University of Pennsylvania). Thorotrast will appear in the cervical lymph nodes of the normal albino rat, as shown by Roentgen ray, about 45 minutes after 0.02 cc. of the substance has been injected into the cerebellomedullary cistern.

Thorotrast, so injected, does not appear in the cervical lymph nodes even after a period of 10 days, if the animals have been shown to have peripheral arterial hypertension following a previous intracisternal injection of colloidal kaolin.

It is suggested that this peripheral hypertension is caused by the increased intracranial pressure. This increased pressure is thought to be due to a block in the channels for lymphatic absorption. The alternative suggestion, that it is due to a persistent meningeal reaction, is considered, but is thought to be unlikely because the leukocytosis in the spinal fluid following the intracisternal injection of kaolin is

present only for the first 3 days and subsides completely by the fifth day. On the other hand, the hypertension seldom appears before the fifth day and usually persists indefinitely.

**The Action of Single Doses of Morphin Sulphate Upon the Movement of the Small Intestine in Man.**—W. OSLER ABBOTT and E. P. PENDERGRASS (Laboratories of Pharmacology and Radiology, and the Gastro-intestinal Section of the Medical Clinic, University of Pennsylvania). Morphin was early observed by fluoroscopy to relax the small intestine, to depress its activity and to delay the motility of its contents. Subsequently balloons in small intestinal "loops" of dogs showed increased tonus and peristalsis. We have combined these methods in normal, intact human subjects. With orally administered balloons recording simultaneously from one or two points between pylorus and cecum, barium is given and the subject fluoroscoped.

*Results.* The duodenum, 2 minutes after 10 to 30 mg. of morphin sulphate is administered hypodermically, contracts forcibly, as shown by a disappearance of barium from the duodenal lumen and by strong compression of the balloon for 20 minutes. Then follows hyperperistalsis of brief duration and thereafter prolonged inactivity. Duodenal stasis and regurgitation, present earlier, disappear. In the ileum there is either slightly increased segmentation or no immediate response. Then the barium gathers into boluses, the gut dilating and becoming less active. The balloons show nothing save a slight transitory rise in tonus at 15 minutes, probably in part due to downward displacement duodenojejunal content. Activity diminishes thereafter. The jejunum reacts in a manner between that of the duodenum and the ileum. Subnormal activity may persist for 24 hours.

**The Measurement of Serum Volume.**—F. WILLIAM SUNDERMAN (John Herr Musser Department of Research Medicine, University of Pennsylvania). In the determination of the serum volume by the intravenous injection of vital red, there is evidence to suggest that complete mixing of the dye in the circulating serum does not occur for 20 to 30 minutes after the injection. If samples of serum are obtained under basal conditions at intervals of 30, 60 and 90 minutes after the introduction of the dye, a linear relationship is obtained which permits extrapolation to the moment of injection and the estimation of the concentration of dye that would have been obtained were complete mixing instantaneous. The quantity of dye injected is measured with precision by means of an especially constructed apparatus. The colorimetric readings are made on undiluted serum in a colorimeter having 2 chambers on each side and fitted with a green monochromatic filter. A simplified procedure requiring only 2 samples of blood is proposed for clinical studies. The procedure gives consistent, reproducible results in normal individuals and reveals differences beyond the normal range in some pathologic cases.

**Nerve Impulses in Single Fibers of the Vertebrate Retina.**—H. K. HARTLINE (Eldridge Reeves Johnson Foundation, University of Pennsylvania). Oscillographic records of action potentials in single optic nerve fibers of the frog's eye have been obtained from small bundles of fibers dissected from the anterior surface of the retina near



the head of the optic nerve. The discharge of impulses in such fibers, in response to illumination of that portion of the retina from which they come, shows considerable diversity, even among fibers from closely adjacent areas of the same eye. In certain of these fibers the response is similar to that in the optic nerve fibers of *Limulus*, showing an initial burst of impulses at high frequency, with subsequent adaptation to a lower level of steady discharge, which is maintained as long as the illumination lasts. In outer fibers, however, the initial burst of impulses is absent, and the discharge builds up slowly (over 1 or 2 seconds) to its steady value. Such fibers show an increase in the impulse frequency when the light is turned off ("off effect"). This is interpreted as post-inhibitory rebound. In another group of fibers it is the maintained discharge which is absent, and the only response is a short burst of impulses when the light is turned on. Such fibers may also show an "off effect," varying from a few impulses to a vigorous burst. In the fourth group of fibers no response at all occurs during illumination, but as soon as the light is turned off a vigorous discharge occurs, initially at high frequency, but gradually dying out. In some cases this discharge may take many minutes to disappear, and occasionally has been observed to break up into a series of rhythmic bursts of impulses. Re-illumination promptly inhibits the discharge in this group of fibers.

It is supposed that this diversity of function among the optic nerve fibers of the frog retina is due to a modification of the original sensory discharge by the neural elements intervening between the sense cells and the optic nerve fibers, and that the various types of discharge will find their explanation in the interplay of excitatory and inhibitory processes in these elements.

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**Correction.**—In the article by Doctors Cohn and Lewis in this JOURNAL (April, 1935, issue) on page 478, lines 5 and 7 from the bottom, and page 481, lines 5 and 8 from the top, the word "weighing" should be "weighting." In the fourth line of the legend of Figure 16 (p. 473), after the word "noted," the word "especially" should be inserted.

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THE  
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ORIGINAL ARTICLES.

ETIOLOGIC AND PATHOLOGIC FACTORS IN POLYCYTHEMIA  
VERA.

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POLYCYTHEMIA vera, first described by Vaquez<sup>1</sup> in 1892 and clearly defined by Osler<sup>2</sup> in 1903, has presented several puzzling features to medical investigators. In all the contributions which have been made in this field many suggestions have been offered to explain the pathogenesis of the condition, but none has served to clarify the problem in spite of the fact that the pathologic physiology of polycythemia associated with pulmonary and cardiac lesions and with the response to an environment found at high altitudes is understood. Excellent summaries of our knowledge of polycythemia, both primary and secondary, have been written by Weber<sup>3,4</sup> and by Harrop.<sup>5</sup>

This report has for its object the presentation of a few observations which may throw some light on the mechanism involved in polycythemia vera and have not been emphasized previously.

In the Hematology Clinic of the New York Hospital it has been noticed that the majority of patients under treatment at present for polycythemia vera were Jews born in eastern Europe (Russia, including Ukrainia, Poland, Austria, Lithuania, Roumania, Czechoslovakia). This suggested a similarity between polycythemia vera and thromboangiitis obliterans. Such a relationship was rendered more probable by the fact that many of the polycythemic patients came to the clinic complaining of symptoms referable to their peripheral vascular systems and were being treated for thromboangiitis obliterans as well as for polycythemia vera.

To study the racial and national incidence of polycythemia vera, the records of six institutions were investigated. These hospitals were selected because the general admission of eastern European Jews was not especially high and because the case histories permitted an accurate differentiation between polycythemia vera and polycythemia secondary to some other condition. The clinics were Bellevue Hospital, Cornell Clinic, New Haven Hospital, New York Hospital, Presbyterian Hospital and St. Luke's Hospital.\* The criteria used to accept a diagnosis of polycythemia vera were a majority of the following: (a) Polycythemia which was distinct and persistent, and which returned after cessation of therapy; (b) splenomegaly; (c) typical red cyanotic appearance of patient; and (d) absence of any other distinct lesion such as pulmonary or cardiac, to explain the polycythemia. The records from the New Haven Hospital were not examined by us but were summarized by Dr. Theodore Klumpp.

TABLE 1.—RACIAL AND NATIONAL ORIGIN OF PATIENTS SUFFERING FROM POLYCYTHEMIA VERA.

Institutions.	Total No. of patients (polycy- themia vera).	Patients of Jewish origin born in eastern Europe (polycythemia vera).		General admission of patients of Jewish origin born in eastern Europe.
		No.	%.	
Bellevue Hospital . . . . .	28	14	50	3 (sample year)
Cornell Clinic . . . . .	7	4	57	12 (estimate)
New York Hospital . . . . .	19	12	63	9 (sample year)
Presbyterian Hospital . . . . .	33	13	39	15 (race not given; eastern European birth)
St. Luke's Hospital . . . . .	34	15	44	7 (race not given; eastern European birth)
New Haven Hospital . . . . .	13	6	46	10 (estimate)
	<hr/> 134	<hr/> 64	<hr/> 47.8	<hr/> 9 (approximate)

The accompanying table gives the results obtained. It can be seen that in each clinic the incidence of polycythemia vera among eastern European Jews was distinctly high. The per cent of

\* We wish to express our gratitude to Drs. Woodruff, Wyckoff, Nammack, Klumpp, Palmer and Wood for permission to study and quote from the records of these clinics.

patients from this group among the general clinic and hospital population could not be obtained in some institutions because such data were not kept. But as far as could be determined the average incidence of eastern European Jews among the general admissions in these hospitals was under 10%. The average incidence of eastern European Jews suffering from polycythemia vera was almost 48% and ranged from 39% to 63% for 134 patients.

The eastern European countries were circularized for information that might give some statistics dealing with the racial incidence of polycythemia. The only country which had any figures was Lithuania.<sup>6</sup> The population of this country is about 2,000,000, of which 155,000 (7.7%) are Jewish. Of 4 cases of polycythemia vera from 1930 to 1934, 2 were Jewish. Professor Julius Bauer<sup>7</sup> of the Allgemeine Poliklinik in Vienna informs us that, although he has no statistics available, he has the impression that polycythemia vera is more common in Jews. Dr. C. W. Baldridge<sup>8</sup> wrote us that in the last 13 years 10 polycythemic patients were treated by the State University of Iowa, Department of Medicine. None of these was Jewish, but the incidence of Jews in the general hospital population is very low and the incidence of foreign-born Jews is probably negligible.

The resemblance of the racial and national incidence of polycythemia vera to that of thromboangiitis obliterans naturally suggested that the bloodvessels of the bone marrow merited study. As far as we could determine no investigation of lesions of the bone marrow vessels has ever been reported. It was thought best to use Masson trichrome stains to obtain good pictures of the bloodvessels. Eosin azure and Giemsa stains were also used. A total number of 69 bone marrow specimens and 4 sections of bloodvessels from amputated limbs of patients suffering from thromboangiitis obliterans and arteriosclerosis were studied.\* The bone marrow was obtained from the sternum in the case of biopsy specimens and from several sources in the case of autopsies, and in the most important cases was fixed in Zenker-formol or in neutral formalin. Of the 69 bone marrows studied 12 were biopsy specimens, of which 5 were from polycythemia vera patients; 2 were from secondary polycythemia (1 patient had pulmonary bronchiectasis and fibrosis, and 1 probably has splenic arteriosclerosis or so-called abdominal thromboangiitis obliterans); the rest from benzol poisoning, aplastic anemia and aleukemic leukosis. The remainder of the bone marrow sections was obtained from autopsy cases. Two of these were from polycythemia vera, 5 from agranulocytosis and the rest from a variety of patients including general arteriosclerosis, cardiac diseases, nephritis, senility, leukosis, malaria, pneumonia. The speci-

\* We wish to thank Drs. Conway and Glenn for performing bone marrow biopsies, and Drs. Curphey, Trubek, Bishop, Olcott, Angevine, R. A. Moore, Helpem and Lawrence Smith for specimens.

mens were obtained from individuals of all ages ranging from infancy to people over 70 years.

The result of these bone marrow studies (see illustrations) showed that in all the polycythemia vera cases there was distinct thickening of the capillary walls and this increase was characterized by a distinct green stain with the Masson trichrome dye, indicating an increase in the fibrous tissue. It should be pointed out that the structures which are designated as capillaries are usually subarteriolar, although some of them may be very small venules because the latter structures have no musculature in the bone marrow. However, these vessels were compared with those of similar size in the control group and had the thinnest walls in the entire section. This capillary thickening was made more evident by the nuclei failing to protrude into the lumen, as is the case with normal vessels. All of the polycythemia bone marrows, except one, showed marked subintimal and adventitial fibrosis of the arteries and arterioles, and in the latter vessels some of the fibrosis extended into and through the media. In 3 of the 5 agranulocytic bone marrows there was some swelling of the capillary walls, but this seemed to be of an edematous nature rather than distinct fibrosis. All of the rest of the bone marrows showed no changes of this type. In the patients suffering from arterio- or arteriolar sclerosis the vessels showed principally medial and adventitial fibrosis; but the capillaries were normal in appearance except that there was a moderate increase of fibrous tissue around them in many cases. As has been pointed out elsewhere,<sup>9</sup> these polycythemic marrows also showed an increase in megalokaryocytes. One polycythemic bone marrow showed distinct thrombosis, both fresh and organized, of some small arteries. This was regarded as significant, since the capillaries in the thromboangiitis obliterans sections showed the same thickening and fibrosis as that seen in the polycythemic bone marrows. One of the most interesting bone marrow specimens was derived from a patient who had been suffering from polycythemia vera for a short time and was considered a mild case. His highest count was 6,500,000 red blood cells, his spleen was only moderately enlarged, he had pain in the calf of his right leg for only 4 months and he responded well to very small doses of acetylphenylhydrazin. Incidentally his brother had a well advanced polycythemic condition. A biopsy specimen of this man's bone marrow showed marked inflammatory and necrotic lesions along the course of his bloodvessels, characterized by a cellular exudate which formed perivascular "cuffs," and some of his capillaries demonstrated thickening in the midst of pronounced inflammatory lesions. The exudate consisted chiefly of lymphocytes and monocytes caught in the migratory elongated phase. A few neutrophils were occasionally found; these rarely formed miliary abscesses.



FIG. 1.—Artery in bone marrow of normal subject. Magnified  $\times 280$ . Practically no fibrous tissue infiltration of wall of vessel.

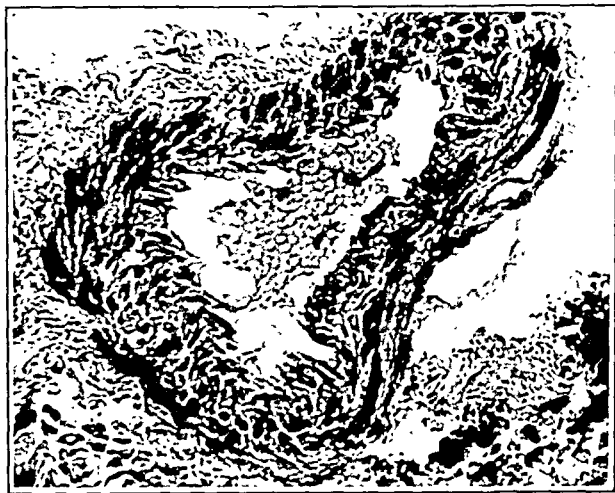


FIG. 2.—Artery in periosteum of arteriosclerotic patient. Magnified  $\times 280$ . Fibrous tissue infiltrating muscularis.

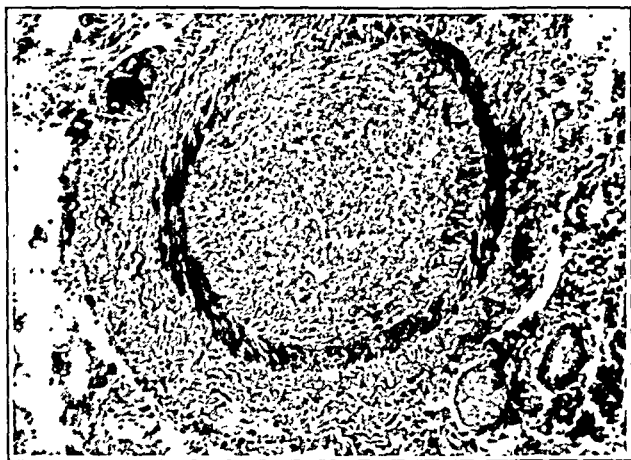


FIG. 3.—Artery in bone marrow of a polycythemic patient. Magnified  $\times 110$ . Marked fibrosis of subintima and adventitia.

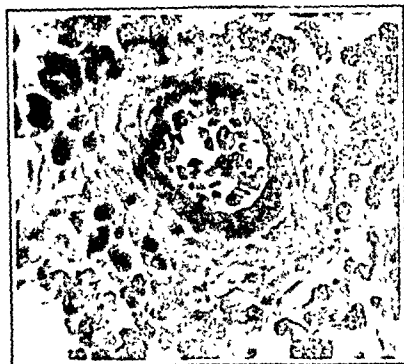


FIG. 4.—Arteriole in bone marrow of normal subject. Magnified  $\times 270$ . No fibrosis in wall of vessel.



FIG. 5.—Arteriole in bone marrow of polycythemic patient. Magnified  $\times 540$ . Fibrous tissue infiltrating entire wall of vessel.

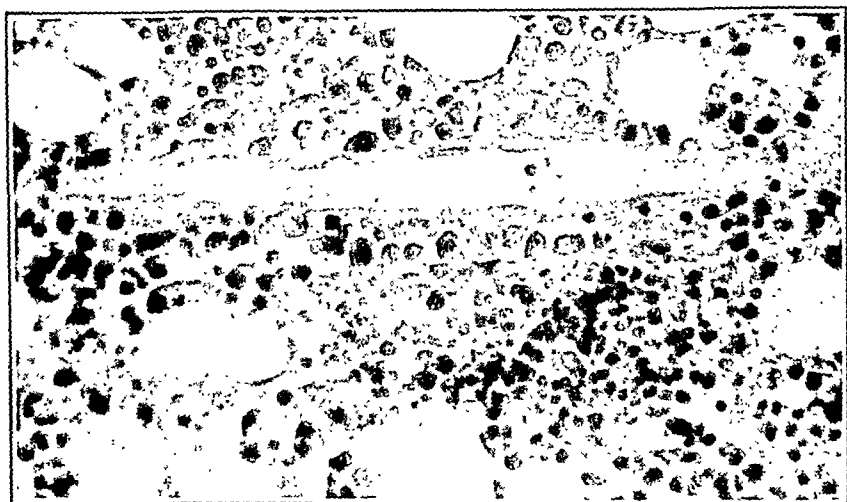


FIG. 6.—Capillary in bone marrow of normal subject. Magnified  $\times 270$ . Thin wall, nuclei bellying into lumen.



FIG. 7.—Capillary in bone marrow of polycythemic patient. Magnified  $\times 290$ . Marked thickening of wall. Cross section of markedly thickened small capillary in field.

**Comment.** The significance of these observations may have various interpretations. As far as the racial and national incidence of polycythemia is concerned, the high incidence among Jews born in eastern Europe applies, of course, only to the cases presented in this study. Whether the same findings will hold true for any other large group of patients will depend upon future studies. However, it is interesting to note that Weber<sup>10</sup> states, "I am myself inclined to the opinion that polycythemia rubra, at all events 'polycythemia hypertonia' (which I regard as a secondary polycythemia), is rather more frequently met with amongst the Hebrew population of Europe than amongst other Europeans." In spite of the fact that Harrop<sup>11</sup> states that this disease is present in all races and has no regional distribution, its predominance in Jews is suggested by Lucas' studies<sup>12</sup> as well as McAlpin and Edsall's case reports.<sup>13</sup> Finally at the recent Congress of the International Association for Geographic Pathology at Utrecht, Professor Anitschkow analyzed 40,000 autopsy reports of arteriosclerosis and intimated that the only definite conclusions from such a study was that vascular sclerosis is probably more prevalent among Jews.<sup>14</sup>

The relationship of these vascular lesions in the bone marrow to polycythemia vera merits further study. It has been suggested that the vascular disease is secondary to the increased 'viscosity' of the blood. Koga<sup>15</sup> describes such a condition in spontaneous gangrene of the extremities and Stern<sup>16</sup> claims that in Buerger's disease a high viscosity of the blood is not an unusual exception with a normal blood count. Schneider,<sup>17</sup> Dietl and Fritz<sup>18</sup> and Münzer<sup>19</sup> have noticed arteriolar and capillary lesions in polycythemia vera in various parts of the body, although they made no bone marrow studies, and suggested that these vascular lesions caused anoxemia of the tissues with secondary overcompensation of the bone marrow. Münzer feels that acute infections such as scarlet fever and typhus may cause general capillary disease. Although Brown, Allen and Mahorner<sup>20</sup> state that they have never seen any association between thromboangiitis obliterans and polycythemia vera, this is not the experience of our clinic, where we find a frequent association. Nor does one gather from Weber's case reports<sup>21</sup> that the combination is rare. In fact, Brown and Giffin<sup>22</sup> report that of 100 polycythemia vera patients, 27 complained of symptoms and demonstrated lesions referable to the extremities (excluding venous thrombosis); 20 were arteriosclerotic, 6 had vasomotor disturbances and 1 was definitely a case of thromboangiitis obliterans. Averbuck and Silbert<sup>23</sup> find that in thromboangiitis obliterans thrombosis of vessels other than the extremities is a very common occurrence.

Almost all students of this subject have been intrigued with the possible relationship of polycythemia vera to anoxemia. It is true that earlier workers<sup>24</sup> regarded this disease as analogous to leukemia.



But this is not generally considered probable because of the maturity of the red blood cells both in the bone marrow and in the peripheral blood. Some observers<sup>25,26,27</sup> considered infection as an important etiologic factor and some familial incidence has long been known. Without much evidence a hormonal defect has also been suggested but by far the most intensive work has concerned itself with the relationship of anoxemia to polycythemia. This is a logical concept because of the known relationship between these two conditions at high altitudes and in cardiac and pulmonary diseases. Harrop<sup>28</sup> suggested that there might be a reduced rate of diffusion of oxygen through the lung and reduced oxygen tension. He said, "If one may assume a very sluggish blood flow in the marrow—small differences in oxygen tension might assume great significance." He found, however, no lesion to account for possible anoxemia, and stated that the "time is ripe for a reinvestigation of the histological findings." Barach and McAlpin<sup>29</sup> believed that polycythemia is not due to anoxemia stimulus because 2 of their patients were kept in an environment of 50% oxygen for 2 weeks without showing any change in red blood cell count, hemoglobin or oxygen capacity. This is evidence against general anoxemia but does not rule out a possible localized anoxemia in the bone marrow. Weber<sup>30</sup> has presented the most interesting opinions, at least so far as this study is concerned. He says "all cases of erythraemia (so-called primary cases) are really only examples of *secondary* or *symptomatic* polycythemia occurring as a result of, or vital reaction towards, some unrecognized obstruction to the circulation of blood in the viscera. The clinical history in erythraemia sometimes furnishes evidence" (of conditions) "which are not unlikely to cause disease and degenerative changes in bloodvessels, leading to circulatory disturbance." "Erythraemia"—(is) "a primary myelopathic disease." The question might then well be raised whether the anoxemic state caused by vascular disease in the bone marrow itself may not be the initiator of compensatory or overcompensatory red blood cell production which results in polycythemia vera.

**Conclusions.** 1. Of 134 patients suffering from polycythemia vera about 48% were Jews born in eastern Europe. The records of these patients were obtained from six institutions in which the average incidence of this racial and national group was under 10%.

2. Seven bone marrow specimens from polycythemia vera patients showed distinct capillary thickening, probably fibrosis, and 6 of these showed in addition marked subintimal and adventitial fibrosis of the subarteriolar capillaries, arterioles and arteries. Of 62 control specimens only 3 of 5 agranulocytic bone marrows gave slight thickening of capillaries, probably due to edema. The rest showed no change from the normal. In the cases of general arterio- or arteriolar sclerosis, medial fibrosis was evident.

3. The vascular changes, especially in the capillaries, of the bone

marrow in polycythemia vera patients suggest the possibility that these lesions may result in anoxemia of the bone marrow with compensatory or excess compensatory polycythemia.

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- (Titles have been omitted for sake of brevity.)

## MACROCYTIC ANEMIA WITH APLASTIC FEATURES FOLLOWING THE APPLICATION OF SYNTHETIC ORGANIC HAIR DYE.

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LONG before beauty culture became a "science," the ancient Persians used vegetable compounds as hair dye. Their methods

\* Dr. Baldridge was unfortunately killed in an automobile accident shortly after submitting this manuscript, which has been revised by his colleague, Dr. W. M. Fowler.—THE EDITORS.

proved to be too tedious and transient for us moderns, so that newer and incidentally more dangerous methods were devised. Physicians have not failed to condemn the use of most modern hair dyes, whether metallic, organic or "compound."<sup>1</sup> Paraphenylenediamin, first prepared by Hoffman, in 1854, formed the key substance for most organic hair dyes until recently, although the use of this substance has been prohibited in some countries because of the skin reactions which it induced.<sup>2</sup>

Except for dermatitis, few intoxications attributable to hair dye have been described in the literature, although it is known that many anilin derivatives exert a deleterious effect on the blood-forming organs. Close<sup>3</sup> reported a case in which involvement of the nervous system was attributed to poisoning by a hair dye of the paraphenylenediamin type, and Haldimann<sup>4</sup> a case in which anemia was apparently due to anilin poisoning.

We have not found any previously reported case in which macrocytic anemia was attributed to hair dye poisoning. Because cases of macrocytic anemia which do not respond to liver therapy are encountered occasionally, the present report is believed to be timely.

The following cases were observed in a period of about 7 months, December, 1933, to July, 1934:

**Case Abstracts.** CASE 1.—M. M., a married woman, aged 42, felt fatigued during 1933, and gradually lost from 167 to 147 pounds in weight. She had dyed her hair in 1932 and had repeated the procedure about 15 times. In October, 1933, she had her hair dyed and a permanent wave put in on the same day. Later in October she began to notice slight bleeding from the nose. From November 16 to 28 the epistaxes were frequent and severe and accompanied by fever, weakness and pallor. After local treatment failed to control the hemorrhages her physician administered horse serum, fibrinogen and calcium gluconate and finally transfusions of 400 cc. of citrated blood were given on each of the 4 days, from November 28 to December 1, 1933. In spite of all treatment the bleeding from the nose continued, and in addition purpuric spots, uterine and urinary bleeding developed.

The patient was admitted to the University Hospital, December 5. There was marked pallor without icterus, the nose was bleeding and crusted, the tonsillar regions were ulcerated and petechiæ and ecchymoses were noted over the body. The spleen was not palpable at the time of admission, but a week later the edge could be felt. The lymph nodes were not enlarged and the gums were not . . . . . The cardiovascular, respiratory and nervous systems were . . . . . was vaginal bleeding and urine obtained by catheter was frankly bloody. The stool was dark and gave a strongly positive test for occult blood.

Examination of the blood revealed: Hemoglobin, 28%, or 4 gm. per 100 cc. (Newcomer); erythrocytes, 1,650,000 per c.mm.; hematocrit, 13.5%; color index, 0.8; volume index, 0.94; saturation index, 0.9;<sup>5</sup> leukocytes, 2550 per c.mm. Differential count: Neutrophils, 46% (band forms, 19; two lobes, 15; three lobes, 12); lymphocytes, 38%; monocytes, 13%; degenerated cells, 3%. The neutrophils all contained toxic granules and some were vacuolated. The erythrocytes varied in size from 5 to 14 microns (ocular micrometer disk). No attempt was made to ascertain the average

diameter of erythrocytes because of marked poikilocytosis and because of the recent transfusions. There was diffuse polychromasia but no stippling was found. The bleeding time was more than 25 minutes; the capillary resistance test was positive; the clot was non-retractile and the platelets measured 0.02% by volume. The coagulation time was 5 minutes and hemolysis of erythrocytes began in 0.42 and was complete in 0.32% sodium chlorid solution. Reticulocytes made up 1.6% of the erythrocytes. The plasma fibrinogen was 0.34%; plasma albumin, 2.28% and plasma globulin 2.1%. The blood calcium was 9.8 mg. per 100 cc. and the van den Bergh was 0.8 mg. per 100 cc. (indirect). The gastric juice was not examined. Roentgenograms of the skull and pelvis were normal. The blood Wassermann reaction was negative.

Bone marrow removed from the upper tibia and suspended in serum suggested a paucity of cells. Neutrophils were virtually absent while myelocytes, myeloblasts and erythroblasts were very scarce.

The findings were those of a severe aplastic anemia and secondary hemorrhagic purpura. The patient was given 1100 cc. of blood as well as daily injections of 5 cc. of coagulen (Ciba). The hemorrhagic tendencies ceased and her recovery in the hospital was slow and uneventful. Hair dye had not been applied since October, 1933, and while I have not had an opportunity to examine the patient's blood since January, 1934, word was received on April 5, 1934, that she was improving steadily. She has since been lost sight of.

The history of the patient was explored exhaustively for exposure to substances which might produce such an aplastic anemia but no probable cause other than hair dye could be found. The patient had applied the dye herself the first time but the results were not satisfactory. She then had several applications of another dye and for the last two or three applications a third dye had been used. The Bureau of Investigation of the American Medical Association informed us that the second dye which the patient used contained paraphenylene-diamin, but that this was not an ingredient of the dye which was applied just before the permanent wave. The same company manufactured both of the latter two dyes and their representative confirmed the above facts concerning paraphenylene-diamin but refused to tell the formulæ for the dyes on the basis that they were trade secrets. Because the dyes almost surely contained anilin derivatives, it was felt that they might be toxic to the blood-forming organs. The changes in the erythrocytes were very suggestive of pernicious anemia but there was no shift to the right in the neutrophils and the patient recovered without liver therapy. There was no history of previous relapses nor paresthesias and no evidence of posterolateral sclerosis nor changes in the tongue.

CASE 2.—A. B., a white woman, aged 47, was married at 19, had a spontaneous abortion at 22 and was divorced at 31. A subtotal thyroidectomy was done at the age of 33, but she entered the University Hospital when she was 43 because of a recurrence of the goiter. Another thyroidectomy was done and in addition a diagnosis of tabes dorsalis with gastric crises was made. From August, 1930, to September, 1932, the patient was admitted to the hospital 4 times and received 13 injections of neoarsphenamin (0.6 gm. each), 6 gm. of tryparsimid and about 30 injections of bismuth. She was inoculated with malaria but had only one chill. During these 2 years blood counts were made on 4 occasions with essentially normal findings. There were no further admissions to the hospital and no more blood counts until 1934, but between September, 1932, and January, 1934, about 60 injections of bismuth were administered by her home physician.

She dyed her hair continually from 1920 to 1934. At first the dye was applied every 3 or 4 months, but the interval between applications was

gradually decreased to 2 months. Permanent waves were never applied until 1930. Once in the summer of 1933 and again in March, 1934, permanent waves were applied a few days after the hair was dyed.

About May 1, 1934, the patient was examined elsewhere and was found to have a macrocytic anemia. The hemoglobin was found to be 70%; erythrocytes, 3,000,000; leukocytes, 5000. Free acid was present in the stomach only after the administration of histamin.

The patient reentered the University Hospital, July 9, 1934, complaining of pain in her back, epigastric distress and weakness. The manifestations of *tubes dorsalis* with gastric crises, syphilis of the aorta, arterial hypertension (blood pressure, 190/120) and a small uterine fibroid were still present, but in addition there was a macrocytic anemia.

Blood examination revealed: Hemoglobin, 55%, or 7.8 gm. per 100 cc. (Newcomer); erythrocytes, 2,900,000; hematocrit, 34%; color index, 0.95; volume index, 1.3; saturation index, 0.7; leukocytes, 700 per c.mm. Differential count: Neutrophils, 50% (band forms, 6; two lobes, 33; three lobes, 10; four lobes, 1); lymphocytes, 23%; monocytes, 12%; eosinophils, 2%; degenerated cells, 13%. The neutrophils contained very few toxic granules. The erythrocytes varied from 7 to 12 microns in diameter (micrometer disk), averaging 9 microns. There was some poikilocytosis and slight polychromasia. Most of the macrocytes were hyperchromic. The appearance of the blood smear was very suggestive of pernicious anemia, except that there was no shift to the right in the neutrophils. The bleeding time was 4 minutes, the capillary resistance test slightly positive, the clot retracted poorly and the platelets were 0.1% by volume. The coagulation time was 7 minutes and hemolysis of erythrocytes began in 0.42% and was complete in 0.32% sodium chlorid solution. Reticulocytes made up 0.5% of the erythrocytes. The van den Bergh was 0.2 mg. per 100 cc. (indirect). Free acid was again present in the stomach after stimulation with histamin.

The patient was given 39 cc. of Lederle's liver extract intramuscularly over a period of 8 days, during which time the daily reticulocyte percentages were as follows: 1.8, 1.2, 1.4, 1, 1.2, 0.6, 0.8 and 0.8. There was no change in either the hematocrit or hemoglobin values after this amount of liver therapy. In February, 1935, her physician reported that she was improved and doing satisfactorily.

A review of the patient's subjective and objective symptoms shows that there were no previous relapses, no paresthesia, no posterolateral sclerosis, no tongue changes, no increase in serum bilirubin and the stomach was capable of secreting hydrochloric acid. The blood examination revealed anemia, leukopenia, a fairly high color index and macrocytosis. There was no response to liver extract.

CASE 3.—B. B., a divorced woman, aged 45, complained of uncertainty in walking, pains in the legs and a girdle sensation around the lower abdomen. She was admitted to the University Hospital, July 20, 1934. The legs were both spastic and ataxic to such an extent that the patient could not walk alone. Two-point discrimination and vibratory senses were greatly decreased in the legs. Plantar extension was present on both sides. The left hand was awkward, the speech tremulous and there was slight euphoria. Dr. Van Epps, of the Department of Neurology, thought that the neurologic changes were more suggestive of multiple sclerosis than subacute combined sclerosis, in spite of the fact that the patient was found to have anemia of the macrocytic type and complete achlorhydria. The patient's blood and spinal fluid gave negative Wassermann reactions but her husband had had a strongly positive Wassermann test. She had had no antisyphilitic treatment.

The hair was dyed first, February 28, 1934, and again in April and in

June. The brand of dye was the same as that which had been used last by Case 1. A permanent wave had been done about 4 hours after the dye was first applied, in February. Shortly after this time the patient noticed that she was becoming pale. All of the neurologic symptoms, except a vague sense of uncertainty on a certain flight of stairs, appeared after the hair was dyed.

Examination of the blood revealed: Hemoglobin, 69% (9.8 gm. per 100 cc.); erythrocytes, 3,070,000 per c.mm.; hematocrit, 35%; color index, 1.1; volume index, 1.3; saturation index, 0.95; leukocytes, 5100 per c.mm. Differential count: Neutrophils, 60% (band forms, 13; two lobes, 26; three lobes, 17; four lobes, 4); lymphocytes, 24%; monocytes, 7%; eosinophils, 1%; basophils, 1%; degenerated cells, 7%. The neutrophils contained only a few toxic granules. The erythrocytes varied from 8 to 12 microns in diameter, the average being 9.5 microns. There was some poikilocytosis and slight polychromasia. Hyperchromia was the rule. After a careful search 1 neutrophil with 7 lobes in the nucleus was found. The changes noted in the smear were typically those of pernicious anemia. The bleeding time was 1 minute, the coagulation time was 4 minutes, the capillary resistance test was negative, the fragility of erythrocytes was normal, the clot retracted and the platelets were 0.5% by volume. The stomach contained no free hydrochloric acid, even after the administration of histamin. The van den Bergh reaction was indirect, 0.4 mg., and bilirubin per 100 cc. of blood

The patient was given 6 cc. of Lederle's liver extract intramuscularly daily for 20 doses. The daily reticulocyte counts with 2 control counts were as follows: 1.2, 1.4, 1.4, 1.5, 1.4, 1.9, 2.3, 2.6, 2.1, 1.6, 2.2, 1.8, 2.2, 2.1, 2, 1.9, 1.3, 1.5, 1.2, 1.1 and 1.9. The hemoglobin and hematocrit values were unchanged after the liver extract but the erythrocyte count had increased to 3,800,000, and the patient felt better. In February, 1935, her physician reported that she was improved and doing satisfactorily.

A review of the patient's subjective and objective symptoms shows that there were no previous relapses, no tongue changes and no increase in serum bilirubin. There were, however, paresthesia, posterolateral sclerosis, anemia, high color index, macrocytosis, leukopenia and achlorhydria.

**Comment.** The first patient was regarded as a probable instance of chemical poisoning for the following reasons:

1. There had been a profound decrease in erythrocytes, platelets and granulocytes with relative increase in monocytes. We had previously noted these changes in a case of chronic benzin poisoning.<sup>6</sup>

2. The hair dye was the most likely source of poisoning elicited.

3. Biopsy of the bone marrow, Roentgen ray and other examinations sufficed to exclude aleukemic myelosis, metastatic tumor of the bone marrow and other causes for myelophthisic or hemolytic anemia.

4. The fact that the patient recovered is perhaps the most conclusive evidence that the anemia and thrombopenia were not myelophthisic in origin. A diagnosis of pernicious anemia was never seriously considered even though the anemia was essentially macrocytic in type.

The permanent wave was applied to this patient on the same day that the hair was dyed the last time. One wonders if the heat and the ammonia water, which are used in the permanent wave process,

might either change the dye chemically or by the induction of hyperemia of the scalp, lead to its absorption in unusual amounts. A preparation which the patient used for washing hair was found to contain tartaric acid and an anilin dye.

Case 2 presents features which add materially to the belief that poisoning by hair dye may produce a macrocytic anemia. The company that manufactured the dye which was used by this patient gave the following information to the Bureau of Investigation of the American Medical Association in 1927. The dye contains no lead, silver or iron and no pyrogallol or paraphenylene-diamin. "The color base is toluylene-diamin, which in the preparation of the dye is so treated and combined with other ingredients in the manufacture as to safeguard, as fully as chemical science is at this time able to do, against possible skin irritation." A representative of this company informed us that no complaint of anemia following the use of their dye had been reported. Intoxication of the bone marrow by syphilis, mercury, bismuth or neoarsphenamin must be considered among the possible causes of the anemia from which this patient suffered. The patient had not received neoarsphenamin for 19 months before the anemia was discovered and the blood count was normal 18 days after the last administration of the drug. Bismuth and mercury are certainly not very likely to destroy hematopoietic tissue. Even if syphilis might produce a blood picture such as was seen in this patient, the changes would not be expected to develop during treatment.

The decreased volume of platelets and the slight neutropenia are noteworthy features, especially in view of the findings in Case 1. The blood findings resemble pernicious anemia more than any other hematologic disease. However, this diagnosis appears to be entirely untenable because of the presence of hydrochloric acid in the stomach, the absence of response to liver extract, the absence of posterolateral sclerosis, tongue changes, remissions, paresthesia and increased serum bilirubin.

The likelihood of pernicious anemia is much greater in Case 3 than in the other cases. While complete achlorhydria is not rare in anemic women of 45, it nevertheless should suggest the possibility of the anemia being pernicious in type. The presence of posterolateral sclerosis even though atypical in some respects would also point to the syndrome of pernicious anemia. In addition to these, we have changes in the blood which are entirely compatible with a diagnosis of pernicious anemia. The absence of tongue changes, the high platelet volume, the lack of increased bilirubinemia and the lack of a characteristic response to liver extract are points against this diagnosis. The reticulocyte count was higher both before and after 20 days of intensive treatment than is usually the case in pernicious anemia. The highest reticulocyte count (2.6%) occurred on the seventh day of liver therapy. This represented an increase of only 1.2 to 1.4% over the control counts.

If this had been a case of pernicious anemia, the expected reticulocyte count, according to Riddle's<sup>7</sup> table, would have reached 3.9% following oral administration of liver. The liver extract was given intramuscularly in order that the reticulocyte response might be as prompt and as pronounced as possible. No attempt was made to determine the presence or absence of Castle's factor in the gastric secretion of this patient. There is still doubt concerning the interpretation of the neurologic changes. It is to be recalled that the symptoms in this patient appeared shortly after the use of the hair dye and that Close<sup>3</sup> reported a case in which there was marked ataxia following the use of a similar dye. His patient recovered after discontinuing the use of the dye.

It is essential that more cases be studied in order to determine the exact relationship between the dye and the blood changes. Likewise, such observation should determine whether or not the changes in the blood and nervous system represent the usual reaction or a form of idiosyncrasy. The part played by the permanent wave must also be established.

It should be remembered that patients with pernicious anemia are likely to lose pigment from the hair at an early age, so that they have this added cause for using hair dye. Therefore, the presence of a macrocytic anemia in a patient with dyed hair does not establish a relationship between the two conditions.

It is possible that the substance which caused the anemia was not the original chemical compound which was applied to the hair, but rather some product which resulted from heating the initial compound. This, together with the fact that animal experimentation is so often confusing when applied to drug idiosyncrasies, or even to ordinary intoxications, has led me to report these cases without attempting to gain laboratory support for the view suggested. Also the opportunity to study human cases is almost unlimited, since a representative of one of the companies states that "thousands of such dual applications (dye and permanent waves) are occurring all over the United States every day."

**Summary.** Three cases of macrocytic anemia are described and discussed in women who had dyed their hair just before the application of permanent waves. In 1 of these the temporary changes in the blood were typical of aplastic anemia.

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## THE NEUROLOGIC ASPECT OF LEUKEMIA.

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INVOLVEMENT of the central nervous system in leukemia is thought to be a rather unusual complication. In some of the standard textbooks of medicine, neurology, and pathology it is mentioned as rare, and in others it is not described. The purpose of this communication, in addition to reporting a case of lymphatic leukemia with an unusual presenting neurologic picture, is to show that the central nervous system is involved frequently, if not in nearly all cases of leukemia, and that such involvement results in clinical signs and symptoms which are frequently overlooked. We believe that the significance of the involvement of the central nervous system in the clinical course of leukemia is comparable in many respects to that in pernicious anemia and plumbism.

The general subject of the neurologic aspect of leukemia and an analysis of 334 cases of leukemia will be discussed after the case report.

**Case Report.** G. K., a 24-year-old married, American fuel oil deliveryman whose past, family, social and occupational histories were entirely irrelevant and uneventful, entered the Boston City Hospital on March 12, 1934 because of difficulty in swallowing of 2 days' duration. Four weeks previously he struck his right shoulder against a truck, which resulted in a stiff and painful upper arm for a week and a residual lameness. Eight days before entry he noted weakness of the left side of the face. In 2 days there was a complete paralysis of this side of the face and loss of taste. For 2 days before entering the hospital he had difficulty in swallowing solid foods. There was nothing else of importance in the history.

**Physical Examination.** A well-developed and well-nourished young male in no pain or distress; alert, intelligent and cooperative. His color was good and there was no fever. The first six cranial nerves were normal. The visual fields, the ophthalmologic examination and visual acuity were within normal limits. There was, however, a complete paralysis of the left seventh nerve involving the forehead, and some weakness of the left palate with an absent gag reflex. No further abnormality in the cranial nerves was noted. The act of swallowing appeared normal. The throat was slightly red, and there was a postnasal discharge. The rest of the physical and neurologic examinations, including a detailed examination of the lymphatic and sensory systems, was entirely within normal limits. The systolic blood pressure was 110 mm. Hg; diastolic, 80.

The white blood count on entry was 14,000; the red blood count, 5,000,000

per c.mm., and the hemoglobin, 95% (Sahli). The differential count showed: neutrophils, 52%; lymphocytes, 40%; monocytes, 4%; eosinophils, 2%. Both the white and the red blood cells appeared normal and there was nothing on repeated examinations to suggest disease in the blood-forming organs. Urine, stool, sputum, throat culture, blood Wassermann, and blood chemistry showed no abnormality.

The patient was thought to be suffering from a left-sided Bell's palsy, but because of the history of difficulty in swallowing and the weakness of the left ninth nerve, a bulbar type of poliomyelitis was also considered.

*Course.* On the 3d day the white blood count had increased to 19,000 without any change in the character of the white cells or in the neurologic or physical condition. Fever was not present. A lumbar puncture was now performed, with the patient well relaxed and lying on his side. A ground-glass, colorless fluid was obtained at a pressure of 150 mm. of water. Dynamics of the spinal fluid were in all respects normal. The fluid contained 1900 lymphocytes per c.mm., and 170 mg. of protein per 100 cc. The chlorid and sugar contents were quantitatively within normal limits. There was a strong midzone rise in the colloidal gold curve. The Wassermann test and the cultures of the spinal fluid were negative. On the 4th day the right seventh nerve became involved, and the patient showed a typical facial diplegia. Symptomatically he was unchanged.

Beginning on the 5th day the patient showed improvement clinically, in that the facial diplegia, together with the weakness of the ninth nerve, gradually cleared. The sensation of taste had returned at the end of the first week and an electrical sensory examination of the tongue was within normal limits. The leukocytosis in the blood persisted, on the other hand, as did the pleocytosis in the spinal fluid. The high-protein content of the cerebrospinal fluid continued, and pressures of from 200 to 250 mm. of water were frequently encountered. The details of the blood and the spinal fluid findings and their relationship are presented in Table 1 and Chart I. Notwithstanding the fact that the patient felt well, had a good appetite and had no fever, a complete neurologic examination was done every day.

On the 10th day the patient exhibited clinical signs of cerebral hypotension: headache, stiff neck, vomiting and a spinal fluid pressure of less than 10 mm. of water. It was thought that the frequent punctures and the need of large amounts of fluid at each tap for the tests had brought on this condition. The syndrome was successfully overcome in a day or two by raising the foot of the patient's bed, forcing fluids by mouth, administering pituitrin intramuscularly and discontinuing the lumbar punctures for 10 days.

On the 33d day the patient walked about his room, feeling perfectly well. The physical and neurologic examinations revealed normal findings except for very slight residual facial diplegia. The blood findings, however, were now suggestive of an early leukemia: hemoglobin, 62%; red blood cells, 3,500,000; white blood cells, 21,000 per c.mm. The differential count showed: neutrophils, 28%, of which 6% were stab forms; lymphocytes, 40%; atypical lymphocytes, 5%; monocytes, 4%; eosinophils, 3%; "blasts," 6%; myelocytes, 7%; nucleated red cells, 4%. There was anisocytosis but very little poikilocytosis or polychromatophilia. Although the basal metabolism was only +3%, the metabolism of the sterile blood (measuring the oxygen consumption of the cells during 24 hours in an incubator) was +23%, as compared with that of two normal subjects, which is also suggestive of a leukemic blood. The spinal fluid at this time showed 400 lymphocytes, a high-protein content, and a normal pressure. On the patient's insistence he was temporarily discharged home for a period of 2 weeks, with the probable diagnosis of leukemia.

At home he was symptomless for 1 week and then developed a severe

headache, vomiting and general malaise. He returned on the 60th day after his first admission, presenting the following clinical picture: There was evidence of loss of weight, and pallor. The fundi showed very full veins, but there were no hemorrhages nor choking of the disks. Except for

TABLE 1.—CHARACTERISTICS OF SPINAL FLUID AND OF BLOOD IN CASE REPORTED.

Day of illness.	Spinal fluid.						Blood.		
	Pressure, mm. H <sub>2</sub> O.	Protein, mg. per 100 cc.	Sugar, mg. per 100 cc.	Chlorid, mg. per 100 cc.	Colloidal gold curve.	White blood cells, per c.mm.	Red blood cells, per c.mm.	White blood cells, thous. per c.mm.	Red blood cells, mills. per c.mm. Hemoglobin (Sahli), per cent.
					<i>First Admission.</i>				
4 . . . .	150	174	..	...	...	1,900	0	18.0	5.0 95
5 . . . .	250	95	60	689	001233200	1,475	0	16.5	
6 . . . .	220	91	..	...	...	560	0	17.5	
7 . . . .	200	126	..	...	...	1,200	0	18.0	
8 . . . .	160	136	59	687	0001221100	1,205	0	19.0	
9 . . . .	70	118	..	...	...	2,500	0	22.0	5.0 90
11 . . . .	80	116	..	...	...	1,900	0	19.0	
15 . . . .	65	...	..	...	...	1,000	0	16.0	
19 . . . .	0	...	..	...	...	1,200	300	17.0	
34 . . . .	130	98	50	689	...	280	0	15.0	
39 . . . .	230	...	..	...	...	410	0	23.0	
42 . . . .	160	...	..	...	...	600	0	18.0	4.3 62
					<i>Second Admission.</i>				
61 . . . .	210	426	63	675	0022344321	4,500	200	20.0	3.0 56
63 . . . .	215	384	..	...	...	4,200	250	22.0	
64 . . . .	310	420	..	...	...	5,200	200		
65 . . . .	250	522	33	633	...	5,000	1,000	26.0	
66 . . . .	250	522	..	...	...	6,200	7,000	22.0	
67 . . . .	280	402	..	...	...	6,200	2,000	32.0	2.0 45
68 . . . .	250	462	55	678	...	5,000	2,000	27.0	
70 . . . .	275	438	..	...	...	4,500	950	23.0	
72 . . . .	250	214	77	658	0111232211	4,000	55,000	20.0	
73 . . . .	280	243	..	...	...	10,000	56,000	13.0	
74 . . . .	240	190	..	...	...				
74 . . . .	170	240	..	...	...	8,000	90,000	8.9	2.3 37
75 . . . .	270	170	..	...	...	2,000	12,000	5.9	
76 . . . .	340	108	..	...	...	1,000	1,750	2.3	
77 . . . .	210	108	78	684	...	500	4,000	1.8	2.0 30
78 . . . .	300	78	..	...	...	500	2,500	1.7	
79 . . . .	210	110	..	...	...	40	2,000	2.0	
80 . . . .	270	106	74	677	0001211000	12	350	1.9	
81 . . . .	150	106	..	...	...	15	350	2.3	
83 . . . .	150	106	..	...	...	7	400	3.0	
88 . . . .	180	132	..	...	...	4	20	10.0	
93 . . . .	170	130	..	...	...	36	2	22.0	3.2 51
95 . . . .	180	120	62	690	0112332110	39	0	29.0	
100 . . . .	165	146	..	...	...	78	0	34.0	
106 . . . .	170	196	..	...	...	220	0	35.0	2.1 36
111 . . . .	190	196	..	...	...	270	0	31.4	
120 . . . .	160	104	..	...	...	30	0	45.0	1.6 30
133 . . . .	220	...	75	702	2334432110	75	0	30.0	

a faint residual weakness of the left seventh nerve, the cranial nerves were without abnormality. The neck was slightly stiff and there was a suggestive Kernig's sign. There was no adenopathy and the spleen was not palpable. The rest of the examination was within normal limits except for an absent right knee-jerk, even on good reinforcement, and generally sluggish reflexes, possibly due to mild acidosis from vomiting. There was no fever.

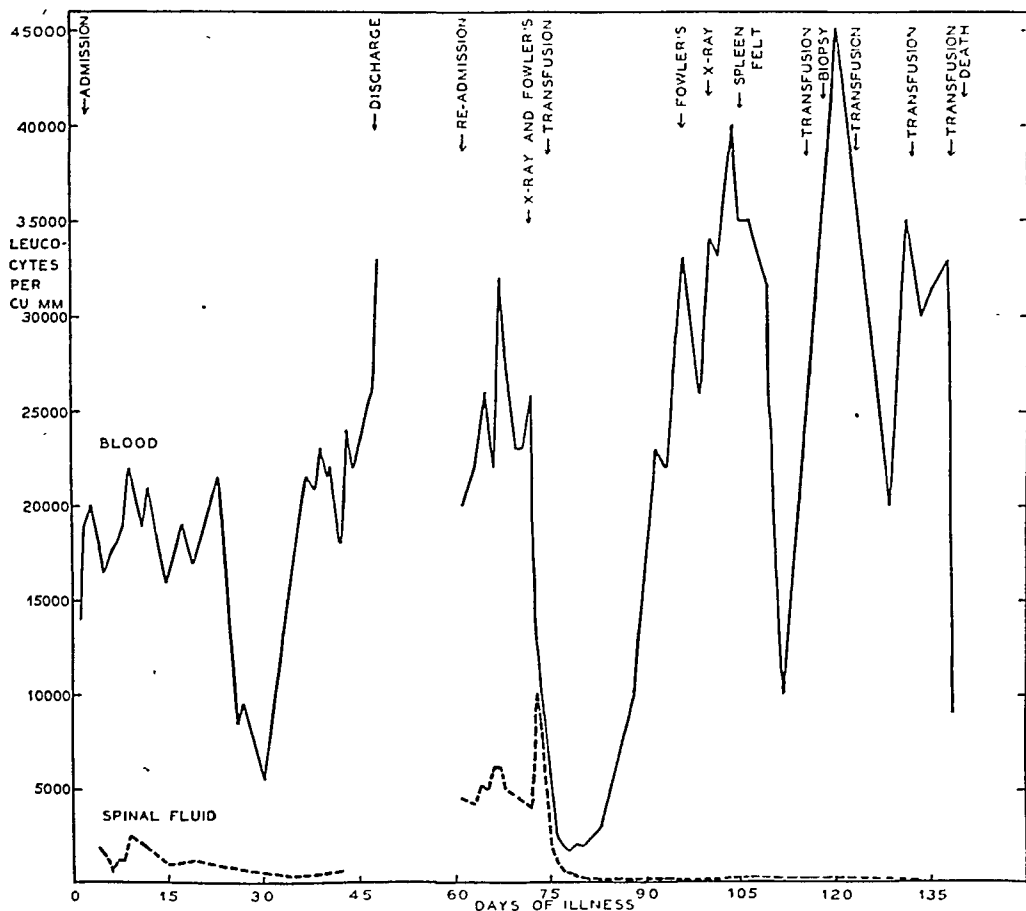


CHART I.—Relation of white cells in blood and spinal fluid in reported case.

The red count of the blood was 3,000,000; the hemoglobin, 56%, and the white count, 20,000. The differential count showed: neutrophils, 13%; lymphocytes, 63%; atypical lymphocytes, 11%; "blasts," 7%; myelocytes, 1%; eosinophils, 2%; nucleated red cells, 2%. Lumbar puncture, done within a few hours after admission, showed a ground-glass fluid containing 4500 cells, all of which were lymphocytes, and a protein content of 426 mg. per 100 cc. The pressure was 210 mm. of water. From this time on, lumbar punctures and blood studies were made almost daily (Table 1 and Chart I). At this time the *definite diagnosis* was made of leukemia, probably of the acute lymphatic type, with invasion of the meninges and cerebrum.

A second measurement of blood metabolism revealed an elevated rate, but the basal metabolism of the patient was still normal. The constant presence of 1000 to 2000 red cells in the spinal fluid during the first quarter of the second admission was the only hemorrhagic sign.

At this time observations were also made on the nature of the low sugar content of the spinal fluid. The comparative glycolytic power of sterile spinal fluid samples was measured. In one series the sugar content of the fluid after puncture was 65 mg. per 100 cc. The sugar content of the fluid which was kept for 24 hours in the incubator without thymol was 33 mg., and that with thymol was 40 mg. per 100 cc. The fluid kept for 24 hours in an icebox without thymol contained 55 mg. of sugar; the fluid from which the cells were centrifuged out and which was then kept for 24 hours in the incubator without thymol contained 63 mg. of sugar. Similar measurements of a second series revealed essentially identical findings, indicating that the low sugar content depended on the glycolytic power of the cells in the spinal fluid.

On the 72d day after the first admission, treatment was started with intravenous Fowler's solution in doses of 10 minims daily with an increment of 1 minim daily, and also deep Roentgen ray treatment over the base of the skull. The response was dramatic. For 2 days the number of cells in the blood slowly decreased, whereas the number of cells in the spinal fluid, both white and red, rose sharply (Chart I). Three days later, however, headaches and vomiting appeared, and the arsenic was discontinued. The next day the patient had a severe chill with a temperature of 102° F. Five days after beginning treatment the white blood count had reached a level of 3000 and there were only 500 white cells in the spinal fluid. Roentgen ray treatment was now discontinued and a transfusion of 500 cc. of citrated blood given, as the red cell count had fallen to 2,300,000 and the hemoglobin to 37%.

For the next 12 days the white cells in both the blood and the spinal fluid remained low; on the 87th day, however, the white cells in the blood began to rise again and in 4 days reached a level of 30,000, whereas the number of white cells in the spinal fluid remained between 25 and 50. The spinal fluid pressure was normal, and the protein content 125 mg. per c.mm. Fowler's solution was now given for 5 days without effect. After an interval of 4 days Roentgen ray therapy was again started, this time without effect. The spinal fluid continued to remain low in cells. Thereafter the patient ran a progressively downhill course.

By the 77th day the basal metabolism had reached a rate of +25%. Cervical and axillary adenopathy was revealed on the 86th day, and the spleen was first palpated on the 108th day. Petechial hemorrhages over the feet and legs, and tarry stools with diarrhea and painful rectum were observed on the 110th day. On the 122d day, for the first time, a crop of fresh retinal hemorrhages were seen in each fundus. On the same day the Roentgen ray plate was interpreted as showing periosteal changes in the orbits. All previous plates of the long bones, chest, pelvis, skull and orbits had been negative.

Roentgen ray treatment over the spleen was attempted, without benefit, on the 130th day. Four more transfusions were given between the 115th and the 138th days, in order to combat the progressive anemia, the red cell counts tending to fall below 1,500,000 and the hemoglobin to 25%. On the 135th day the patient developed a *S. hemolyticus* infection at the site of one of the transfusion cannula wounds. He began to bleed from the mouth and the renal tract, in addition to having bloody stools. The white blood count rose to 5000 lymphocytes, with less than 10% of the cells of these very toxic in appearance. No new neurologic signs developed, but there was a temperature of 102° to 103° F. Death followed 139 days after the first observation. The patient remained clear mentally to the end and seemed to die from exhaustion and hemorrhage.

*Necropsy.* A complete postmortem examination was done 1 hour after death (Dr. Robert Williams). The skin showed numerous purpuric spots

2 mm. in diameter and had a slight icteric tinge. There was no excess of fluid in the serous cavities, but the serous membranes in the three cavities were studded with pin-point hemorrhages. The heart was normal except for a small hemorrhage into the anterior cusp of the mitral valve. The lungs showed small hemorrhages at the posterior part of each base. The tracheal lymph nodes were slightly enlarged. The liver and spleen were enlarged. The esophagus and the stomach were normal, but the small and the large intestines, including the rectum, contained many pin-point hemorrhages. The kidneys had many small hemorrhages throughout their substance and there was bloody urine and fresh hemorrhages in the bladder. The brain and cord were grossly normal and each retina had several hemorrhages 1 to 2 mm. in diameter. The bone marrow was bright red.

*Histologic Examination.* Heart muscle and pericardium, lungs, bronchial walls and pleura were studded with small foci of very young, as well as mature lymphocytes. Similar foci were also found in the pancreas, kidneys, small and large bowels, rectum, spleen, liver, adrenals, lymph nodes, adventitia of the aorta, sternal and femoral marrow and skin. The eye showed similar infiltration of the optic nerve sheath, sclera and retina, in addition to many large and small hemorrhages in the retina. The meninges of the brain and cord were rather diffusely infiltrated with scattered foci of very young and of adult lymphocytes, but showed no sign of hemorrhage or of other type of meningeal reaction. The cerebral tissue itself contained scattered minute foci of very small lymphocytes without perivascular infiltration or hemorrhage. The cerebellum, remarkably, was free of change. Hematoxylin and eosin sections showed infiltrations of the posterior roots of the cord with young and with adult lymphocytes. The cord substance itself was normal except that in some areas occasional round cells were seen near the anterior roots. Oxidase stain of various tissues invaded with these cells showed that they were of the lymphocytic series. *The anatomic diagnosis was acute lymphocytic leukemia.*

**COMMENT.** The significance of the observations described in this case lies not only in the remarkable clinical features, but also in the fact that detailed clinical and laboratory observations were made from a relatively early stage of this disease to its termination. The unusual feature of this case was the early appearance of neurologic signs with remarkable changes in the spinal fluid before any abnormality could be ascertained in the appearance of the blood cells, in the spleen, the lymph nodes, or in the basal metabolic rate. Whether or not the nervous tissue was first involved it is not possible to state, as changes in the central nervous system might have caused more demonstrable clinical signs than changes in other organs.

It seems to us quite remarkable that there was no evidence of bleeding within the central nervous system, either clinically during the hemorrhagic phase or microscopically at postmortem.

The leptomeninges were probably the source of the lymphocytes in the spinal fluid, as they were the most prominently involved part of the nervous system at autopsy. The high spinal fluid protein is difficult to interpret. It will be shown later that abnormally high protein values are not infrequently found in the spinal fluids of cases of leukemia with central nervous system complications. Neoplastic tissue in contact with the pia-arachnoid is known to be the

source of very high protein content in the cerebrospinal fluid, and this is a valuable diagnostic aid in determining the presence of brain tumor. A similar mesodermal reaction which we believe to exist in leukemia might also raise the protein content considerably. The occasional low spinal fluid sugar values in this case are explained by the high glycolytic power of the leukemic cells in the fluid.

**Clinical Manifestations of Involvement of the Central Nervous System in Leukemia.** The literature on the subject of leukemia with central nervous system involvement includes, as far as we have been able to ascertain, 146 cases, reported by 75 authors (38 in German, 17 in American, 8 in English, 7 in French, 2 in Italian, 1 in Spanish, 1 in Swedish, and 1 in Russian literature). Since the first case described by the anatomist Burns in 1823<sup>1</sup> as a strange growth in the brain, probably a case of cerebral chloroma, the number of cases reported has steadily increased. Out of 38 cases of chloroma reported in the literature, Dock and Warthin, 1904,<sup>2</sup> found 13 cases with cerebral and spinal involvement, and to these they added 1 case of their own. Baudouin and Parturier, in 1910,<sup>3</sup> and Tapie and Cassar, in 1919,<sup>4</sup> gave excellent summaries of the French literature. In 1926 Fried<sup>5</sup> summarized 30 cases—mostly from the German literature—in addition to reporting 1 of his own. In 1927 Trömmner and Wohlwill<sup>6</sup> reported careful microscopic examinations of the postmortem material from 12 cases of leukemia, 9 of which had manifested no neurologic signs or symptoms. They found, nevertheless, that 11 (91%) had microscopic evidence of invasion of the central nervous system. Ten of their cases showed invasion of the dura at the Gasserian ganglion; in only 1 case, however, was there a typical trigeminal neuralgia. These authors suggest that the fifth nerve should be tested in all cases of leukemia. Viets and Hunter, in 1933,<sup>7</sup> described 4 cases of lymphatic leukemia with involvement of the central nervous system. The spinal symptoms and pathology in leukemia were studied by Critchley and Greenfield,<sup>8</sup> in 1930. Diamond,<sup>9</sup> in 1934, published an excellent micropathologic study of 14 cases that he had examined, 7 of which showed no neurologic signs. In this paper Jaffé pointed out that leukemia does not involve the nervous system as a metastasis, but that the involvement represents the response of the neurologic mesoderm to a general disturbance of mesoderm throughout the body. The rest of the literature analyzed consisted chiefly in clinical and pathologic case reports combined with bibliographic references.

The type of neurologic lesion in the 146 cases reported in the literature, 89% of which came to postmortem examination, are presented in Table 2. The classification is based on the most significant presenting lesion, as found at postmortem, or as indicated by the clinical signs of those few cases without necropsy. In many of the cases (30%), however, more than one part of the nervous system was involved. The 23 cases with cranial nerve

palsies included 17 cases of seventh nerve paralysis with 12 instances of diplegia, and 7 cases of sixth nerve palsies with 5 diplegias. One of the 7 cases had both sixth and seventh nerve palsies. The eighth, ninth, tenth, eleventh and twelfth cranial nerves were the least frequently involved.

TABLE 2.—NEUROLOGIC LESIONS IN 146 CASES OF LEUKEMIA REPORTED IN THE LITERATURE.

Type of lesion.	No. of cases.	Per cent of total.
Cranial meninges . . . . .	26	17.8
Cranial nerve nuclei . . . . .	23	15.7
Cerebral invasion . . . . .	23	15.7
Cerebral hemorrhage . . . . .	47	32.2
Peripheral nerve . . . . .	2	1.4
Spinal meninges . . . . .	10	6.9
Spinal cord invasion . . . . .	12	8.2
Spinal cord hemorrhage . . . . .	1	0.7
Spinal extradural . . . . .	2	1.4
Total . . . . .	146	100.0

It is of special interest that the pathologic reports of Trömner and Wohlwill<sup>6</sup> and of Diamond<sup>9</sup> indicate that in leukemia a very high proportion of cases (over 90%) show microscopic involvement of the central nervous system. Between 50 and 75% of the cases, however, show no neurologic signs during life, suggesting that from 25 to 50% of all cases of leukemia should exhibit some clinical sign of neurologic involvement.

We have accordingly analyzed for neurologic signs and complaints the records of all the leukemia cases at the Boston City Hospital during the last 20 years (240 cases), at the Huntington Memorial Hospital during the last 10 years (67 cases), and at the Massachusetts General Hospital during the last 5 years (27 cases): a total of 334 cases. It was found that 20.5% had neurologic complications, excluding retinal lesions. It is to be regretted that in only 3.3% had postmortem examinations of the central nervous system been performed, and in none were careful serial sections made. It is impossible to classify the cases on an anatomic basis and to correlate the neurologic findings. We have grouped them according to the symptoms and signs. Tables 3 and 4 show the details of these find-

TABLE 3.—INVOLVEMENT OF THE NERVOUS SYSTEM IN 334 CASES OF LEUKEMIA RECORDED IN 3 BOSTON HOSPITALS.

	Number.	Per cent.
Total cases . . . . .	334	
Postmortems . . . . .	55	16.4
Postmortems of central nervous system . . . . .	11	3.3
Involvement of central nervous system* . . . . .	69	20.5
Retinal hemorrhage . . . . .	38	11.4
Ophthalmoscopic examination . . . . .	127	38.0

\* These figures are based on clinical manifestations and do not include cases with retinal hemorrhage.



ings. It is of interest that the most frequent neurologic manifestations were cranial nerve palsies or anesthetics. Unilateral or bilateral involvements of the seventh and sixth nerves were most frequently encountered. It is probable that with greater appreciation of the neurologic complications in leukemia the incidence of neurologic symptoms and signs will be found to be higher than the 20.5% obtained from the records.

TABLE 4.—NEUROLOGIC SYMPTOMS AND SIGNS IN 69 CASES OF LEUKEMIA RECORDED IN 3 BOSTON HOSPITALS.

Clinical manifestations.	No. of cases.	Per cent of total.
Cranial nerve palsies or anesthesia . . . . .	21	30
Absent reflexes . . . . .	13	19
Pyramidal signs . . . . .	8	12
Paresthesias . . . . .	10	14
Herpes . . . . .	4	6
Meningeal signs . . . . .	5	7
Miscellaneous: Coma, paralysis, tremors . . . . .	8	12
Total . . . . .	69	100

In order to ascertain whether neurologic signs are more apt to occur in one form of leukemia than in another, the incidence of neurologic manifestations has been analyzed in the various types of leukemia of the Boston group of cases, as well as of the cases with neurologic involvement reported in the literature. Obviously, the classification of leukemias was not feasible in all instances; the latter group, as well as instances of chloromas, is included in the "miscellaneous group" of Table 5. The data presented in this table indicate that neurologic complications are apt to occur with about equal frequency in acute and in chronic forms of leukemia, as well as in lymphatic and in myelogenous types.

TABLE 5.—NEUROLOGIC INVOLVEMENT IN DIFFERENT TYPES OF LEUKEMIA.

Type of leukemia.	Total cases.		Involvement of central nervous system.		Retinal involvement.	
	No.	%.	No.	%.	No.	%.
Three Boston hospitals (334 cases)						
Acute lymphatic . . . . .	62	18.5	14	22.6	14	22.6
Chronic lymphatic . . . . .	80	23.9	17	21.2	8	10.0
Acute myelogenous . . . . .	58	17.3	13	22.4	8	13.8
Chronic myelogenous . . . . .	91	27.2	21	23.1	7	7.7
Miscellaneous group . . . . .	43	12.9	4	9.3	1	2.3
Reported in literature (146 cases):						
Acute lymphatic . . . . .	29	19.8	29	100.0		
Chronic lymphatic . . . . .	17	11.6	17	100.0		
Acute myelogenous . . . . .	21	14.4	21	100.0		
Chronic myelogenous . . . . .	22	15.1	22	100.0		
Miscellaneous group (including 21 cases of chloroma) . . . . .	57	39.0	57	100.0		

*The Cerebrospinal Fluid in Leukemia.* Little is known of the changes in the cerebrospinal fluid in leukemia, since in many of the cases reported in the literature lumbar punctures were not done. Of the 146 cases reported, only 23 had lumbar punctures and 1 a ventricular puncture (15.8%). Five of the 24 had two lumbar punctures, 1 had four, and 2 had combined cistern and lumbar punctures for leukemic spinal block. There are, therefore, in the literature altogether 35 examinations of specimens of spinal fluid. In none of these cases, however, was the fluid adequately studied. Of the 24 cases with spinal tap only 6 (25%) showed normal fluid with respect to pressure, protein and cell content. In 9 of the 24 cases (37.5%) there was an increase in the cellular elements. Hall's case of chloroma had 120 lymphocytes "per sixth field" but was described as cloudy.<sup>10</sup> In Hill's case the ventricular fluid contain 370 lymphocytes,<sup>11</sup> and in Barker's, 267 myelocytes.<sup>12</sup> Litterer reported a case with cloudy fluid with 80% myelocytes,<sup>13</sup> and Schwab a case with bloody fluid.<sup>14</sup> In the patient studied by Mieremet, the second tap revealed 34 lymphocytes.<sup>15</sup> Heissen's case had 375 myelocytes in the fluid of the first tap and none 10 days later.<sup>16</sup> Munro reported 4 taps on his case of meningeal leukemia with bloody fluid each time.<sup>17</sup> Viets observed 1 case of acute lymphatic leukemia with 750 lymphocytes and meningeal signs.<sup>7</sup>

In 10 cases there was increased protein qualitatively, as measured by the Pandy or Nonne-Apelt tests, and in 4 there was a quantitative increase—a total of 58.3%. Three of the 10 cases exhibited signs of block as a result of leukemic myelitis, but in 1 of these the fluid drawn from the cistern was, nevertheless, normal in protein. The spinal fluid pressure was high in 8 of the 24 cases, it was not mentioned in 4, and was normal in the rest. Bacterial cultures in 5 were negative. Sugar contents were normal in the 3 cases in which this test was done. No chlorid determinations were reported. Five cases showed midzone rises in the colloidal gold curve. The Wassermann reaction was negative in the 17 cases in which it was tested.

Among the 240 cases of leukemia at the Boston City Hospital there were 41 cases with signs referable to the central nervous system, excluding retinal hemorrhages. There were but 6 cases in which lumbar punctures were done (Table 6), not including the case here reported, in which repeated detailed studies of the spinal fluid were made. Of the total 7 cases with spinal tap, the fluid was entirely normal in 2, in 1 with active syphilis it contained 18 lymphocytes, and in 1 there were 500,000 red blood cells and a protein content of 524 mg. per 100 cc. The remaining 2 showed only high pressures with normal protein and cell contents. There was 1 additional case on which lumbar puncture was not done, but which at postmortem examination 4 hours after death showed 12,000 lymphocytes in the ventricular fluid. Control observations in post-mortem spinal puncture showed only from 10 to 20 large cells.

TABLE 6.—SPINAL FLUIDS IN 10 CASES OF LEUKEMIA COLLECTED BY THE AUTHORS.\*

No.	Type of leukemia.	Pressure, mm. H <sub>2</sub> O.	Protein, mg. per 100 cc.	Cells (lympho- cytes), per c.mm.	Colloidal gold curve.
1	Chronic lymphatic	250	32	2	0000000000
2	Acute myelogenous	...	Negative	3	
3	Chronic myelogenous	320	28	0	0000000000
		250	32	0	0000000000
4	Acute myelogenous	...	18	0	0000000000
5	?	Normal	...	18	
6	Chronic myelogenous	Low	524 (Yellow)	500,000 (R. b. c.)	
7†	Acute lymphatic	200	120	500	2334432111
8	Chronic lymphatic	100	30	3	0000000000
9	Acute myelogenous	450	+++	22	5443322100
		450	110	12	
10	Acute myelogenous	80	+++	170	

\* Cases 1 to 7 are from the Boston City, 8 and 9 from the Massachusetts General, and 10 from the Huntington Memorial Hospital.

† These figures represent the average of 40 lumbar punctures done on our reported case.

In the 67 cases of leukemia at the Collis P. Huntington Memorial Hospital during the last 10 years, one lumbar puncture was done in a case of meningeal leukemia. The spinal fluid showed 170 lymphocytes, increased protein, and a weakly positive spinal fluid Wassermann. Necropsy revealed no evidence of syphilitic involvement of the central nervous system, but there was an extensive meningeal leukemic infiltration. Of the 27 cases of leukemia at the Massachusetts General Hospital, 2 had lumbar punctures, 1 with normal and 1 with abnormal findings. The details of the spinal fluid examinations of the Boston cases are presented in Table 6.

Thus, 24 patients who had had lumbar punctures were collected from the 146 cases of leukemia with central nervous system involvement reported in the literature. To this number, 10 were added from 334 cases of leukemia studied at the Boston City Hospital, the Massachusetts General Hospital and the Huntington Memorial Hospital. Of this total of 34 cases available, only 9 (26.4%) had normal spinal fluids. The most frequent abnormalities of the cerebrospinal fluid were in the protein content (in 52.9% of the cases); the pressure (35.3%) and the cell content (41.4%). The changes occurring in the spinal fluid of patients with leukemia are best illustrated by the numerous observations in the case here reported, which is the first instance in which the spinal fluid was adequately studied over a prolonged period.

In all cases of leukemia neurologic examination and lumbar puncture should therefore be done. Neurologic signs and changes in the spinal fluid may at times be the only diagnostic feature of the case. Examination of the spinal fluid should include manometric pressure readings, total and differential cell count, and quantitative protein, sugar and chlorid values. If any abnormality is found, repeated

taps are indicated. Even with a normal initial fluid, lumbar punctures should be done from time to time.

**Summary.** 1. The clinical course of an unusual case of acute lymphatic leukemia is reported. The presenting manifestations were facial diplegia and a spinal fluid, under elevated pressure, containing 2000 cells and increased amounts of protein. The usual clinical manifestations, including the blood picture, developed later, over a period of 10 weeks. The relationship between changes in the spinal fluid and changes in the blood has been systematically studied.

2. An analysis of the literature of the past 50 years has revealed 146 cases of leukemia with neurologic signs, excluding retinal involvement. It is estimated that only about 25% of cases with histologic evidence of leukemic infiltration of the central nervous system exhibit neurologic signs.

3. An analysis of the records of 334 cases of leukemia in Boston revealed an incidence of 20.5% with neurologic signs, excluding retinal lesions. The frequency of neurologic complications in the acute and chronic types of leukemia, and in the lymphatic and myelogenous types, was about the same.

4. The most frequently observed neurologic signs were unilateral or bilateral palsies of the seventh and sixth nerves, with less frequent involvement of the fifth, eighth, ninth, tenth, eleventh and twelfth nerves. Absent deep reflexes, pyramidal signs, paresthesias and signs of meningeal irritations have also been encountered. The neurologic signs, and particularly involvement of the cranial nerves, often exhibit rapid fluctuations.

5. In 73.6% of 34 cases the spinal fluid showed abnormal findings, as indicated by increased cell count, by increased protein content, and by elevated pressure.

6. In view of the frequent involvement of the central nervous system, systematic neurologic examination of the patients and study of the spinal fluid can be of aid in the diagnosis and management of patients with leukemia.

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(Owing to lack of space, the complete bibliography of the subject is not included here.)

## FATAL ETHYLENE DICHLORID POISONING.

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ETHYLENE dichlorid, the first known of the ethylene-halogen compounds, was discovered in 1795 by Dutch chemists who named it "Dutch liquid." The formula is  $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$ . It is not to be confused with dichlorethylene  $\text{CH}_2=\text{CCl}_2$  and  $\text{CHCl}=\text{CHCl}$  from which it differs chemically as well as pharmacologically, especially in its action on the eye (Steindorff<sup>1</sup>).

Ethylene dichlorid was first used as an anesthetic (Nunneley, Simpson, Snow<sup>2</sup>) in 1848-1849 (Eulenberg<sup>3</sup>). In 1879, a committee of the British Medical Association<sup>13</sup> reported on the use of ethylene dichlorid as an anesthetic after experimentation on rabbits. Just when this substance ceased to attract attention as an anesthetic is not certain, but it is likely that the discovery, in 1887, by DuBois and Roux,<sup>4</sup> that it caused corneal opacities was a factor in its being discarded. In recent years ethylene dichlorid has found many new uses. The fourth edition of *Merck's Index*<sup>5</sup> listed it as an anesthetic, rubefacient and antispasmodic; it stated that it is used internally for general anesthesia, cramps and diarrhea and externally as a solvent for iodine (for skin disinfection), fats, oils, gums, resins and

esters. The maximum dose is stated as 1 cc. for single dose and 3 cc. per day.

Today ethylene dichlorid is used commercially chiefly as a solvent; in cleaning fluids and lacquers it has a wide and increasing application. It has been used to kill moths and weevils, the latter in the fumigation of grain and flour. In a mixture with carbon tetrachlorid it has been employed as a fumigant and a fabric cleaner. Sayers, Yant, Waite and Patty<sup>6</sup> stated that ethylene dichlorid has been cited as a stimulant for sprouting potatoes. The inhalation of ethylene dichlorid is an important problem in industrial hygiene. It is strange that in spite of its extensive commercial use, no cases of ethylene dichlorid poisoning after oral ingestion have apparently been reported previously.

**Case Report.** S. E., male, aged 63, accidentally drank upon an empty stomach 2 ounces of ethylene dichlorid which he has mistaken for gin and had mixed with orange juice and ginger ale. No immediate effects were felt. No alcoholic beverages were taken before or after drinking the ethylene dichlorid. Two hours later he began to feel nauseated and faint and started to vomit during the following hour. When he arrived at the hospital, 5 hours after the accident, he appeared dazed and distressed and was unable to stand. He vomited a liquid that resembled milk, which had been given to him by his family physician 3 hours before. Because the impression had been given that the fluid which he had drunk contained mercury, his stomach was lavaged with 2 quarts of milk; 8 ounces of mineral oil were left in his stomach.

On *physical examination* the blood pressure in the right arm was 152/84, in the left 136/82. The biceps, triceps and patellar reflexes were active. The skin of the body was pale, cool and dry. The face was cool and moist. The lips were slightly cyanosed. There was no jaundice. The conjunctiva was moderately injected. The extraocular movements and accommodation were normal. The pupils were dilated and equal. In bright light they constricted slightly and momentarily. The corneas were clear. The odor of the breath resembled that of chloroform but had also a pungent quality. The tongue had a heavy yellow coating. The upper pharynx was injected. Coarse râles were heard over the lung bases. The heart sounds were distant. The left radial pulse was not palpable, while the right was normal. His rectal temperature was 96.2° F., his pulse 72 and respiration 20. He continued to vomit an opaque yellowish fluid mixed with oil. He was given 750 cc. of a 10% glucose solution intravenously. A blood count taken during the night, 8 hours after the accident showed: Erythrocytes, 5,260,000; leukocytes, 11,800; 86% neutrophils (32 filamented and 54 non-filamented), 11% lymphocytes, 3% monocytes; no reticulocytes; no abnormality of erythrocytes. A urinalysis of the 16 ounces of urine voided at about this time showed: Specific gravity, 1.028; acid reaction, yellow flocculent sediment; moderate albumin; 4+ sugar; no acetone; no diacetic acid; bile salts present; bilirubin present; no urobilin; few hyalin and granular casts; no erythrocytes, no mucus, crystals or cylindroids. Seven dark brown liquid stools were passed during the night. The patient felt during this period as though he were intoxicated on alcohol except that there was no euphoria. The examination of 6 ounces of urine voided during the early morning hours showed a specific gravity of 1.009; alkalin reaction; turbid, abundant albumin, 3+ sugar; no acetone, diacetic acid, casts or erythrocytes; 5 to 7 white blood cells per high-power field; no epithelial cells, few mucous

shreds; many triple phosphate crystals; no cylindroids. He complained of a pain in his lumbar spine and later in the right lower abdomen. His rectal temperature taken during the morning hours was 99.6° F., his pulse 108 and his respiration 30. A van den Bergh test at this time showed that the direct reaction was biphasic and the indirect reaction was 4.6 units. He was drowsy and did not answer questions. Soon afterward his hands and face became cyanosed; pulse and heart sounds could not be obtained and his respiration became more labored. In spite of administration of adrenalin, atropin sulphate, caffein sodiobenzoate subcutaneously and the use of an oxygen tent the patient died 22 hours after the accident.

On *postmortem examination* (W. C. Hueper; 3 hours after death) the pleura was smooth and glistening with the exception of a few old adhesions at both apices. The lungs were well distended, grayish-red, moderately anthracotic. The lower lobes had a fleshy consistency in places and were of a darker red color. The cut surface was reddish in the upper lobes and bluish-red in the lower lobes. Dark red blood was oozing freely from the cut surface. The bronchi were free and had a velvety smooth mucosa.

The heart was normal for small foci of sclerosis and calcification in the wall of the coronary vessels. The aorta showed a moderate degree of sclerosis.

The peritoneum was smooth and glistening with no free fluid. The gall bladder, pancreas, suprarenal glands, testicles, prostate, seminal vesicles and the marrow from the femur, rib and lumbar vertebrae were normal.

The liver weighed 1600 gm. and measured 26 by 22 by 6.5 cm. Several deep respiratory sulci were found over the right lobe. The surface was smooth and showed a reddish-brown mottling with a few distinct yellow areas. Blood exuded freely from the cut surface which showed many irregular, small yellow areas.

The spleen weighed 200 gm., and measured 13 by 3.5 by 8 cm. The capsule was gray and smooth. The organ was firm and showed on the cut surface distinctly outlined follicles embedded in a dark red pulp.

The kidneys had moderately adherent capsules. The right organ weighed 170 gm. and measured 13 by 5 by 3.5 cm., left weighed 180 gm. and measured 13 by 6 by 4 cm. There were many small cysts and several coarser retractions present in the grayish-red cortex. The cut surface showed a reddish-gray cortex with fine red radiating stripes and well-demarcated, grayish-purple pyramids.

The esophageal mucosa was smooth and gray. The stomach held a large amount of a grayish-yellow, turbid liquid containing oil droplets and white floccules. The mucosa was slightly folded, swollen and grayish-red. There were no hemorrhages or ulcerations. The mucosa of the duodenum, jejunum and ileum showed a similar picture. Small red spots were present in the lower part of the mucosa of the ileum. The subserous vessels of the distended intestine were injected. The degree of hyperemia increased toward the cecum. The intestinal lumen was filled with a reddish-brown fluid. The large bowel was reddish-purple and contained a light brown, semifluid material. The mucosa of the cecum, ascending, transverse and upper part of the descending colon was markedly swollen and of deep red color.

The vessels of the pia arachnoid were markedly hyperemic. The brain weighed 1450 gm. The cut surface of the brain was hyperemic with abundant oozing of blood from the cut vessels. There was no macroscopic evidence of hemorrhages. The amount of fluid in the lateral ventricles was somewhat increased.

*Microscopic Examination.* The myocardium showed a moderate and diffuse infiltration with lymphocytes which sometimes formed small perivascular accumulations. The muscle cells appeared normal.

The alveoli of the lungs were distended in places and formed smaller

cavities caused by the rupture of the interalveolar septa. Alveoli located adjacent to these emphysematous regions appeared to be compressed. The vessels were filled with blood and the larger ones contained numerous leukocytes.

The bloodvessels and capillaries of the liver were distended, filled with erythrocytes and numerous leukocytes. Small hemorrhages were occasionally seen. Fatty degenerated cells were present in moderate number, especially in the periphery of the lobules.

In the *pancreas* many areas of fat tissue were found scattered in the normal parenchyma.

The *spleen* showed a marked distention of the sinuses and pulp spaces with erythrocytes. The follicles were normal.

The cortex of the kidneys showed a few arteriosclerotic scars. The tubular epithelium in the cortical region had partly lost its nuclei, a granular pinkish material filling the lumina. The lumina of the pyramids contained bluish-stained casts. Those of the papillary portions were completely necrotic in some areas, having become incrustated with calcium salts evidenced by the intensely blue staining of the cellular debris. The surrounding tubular elastic membranes, which filled in part the collapsed lumina in curl-like formations, and elastic membranes of adjacent smaller vessels were also calcified. Bluish coarse granules were seen in the cytoplasm of some tubular epithelial cells, pointing to the causative mechanism of the calcifications present in the surrounding renal tissue. The apparently well-preserved tubular epithelial cells contained on the other hand not infrequently a coarse, granular, brown pigment.

*Suprarenal glands* and *testicles* were normal.

Sections from the *colon* showed a complete absence of epithelial lining; only in the glandular invaginations was it well preserved. The loose connective tissue of the mucosa showed a marked imbibition of erythrocytes mixed with a moderate number of leukocytes which were mainly of the mononuclear and immature neutrophilic type. The vessels of the submucosa were engorged and contained numerous leukocytes. There was a diffuse erythrocytic infiltration in the submucosa. A marked vacuolar and granular degeneration with a loss of the normal longitudinal striation and cell structure was present in the muscularis. Sections from the *ileum* revealed a marked leukocytic infiltration of the mucosa and extensive granular degeneration of the muscularis. The submucosa was hyperemic and edematous. The cells of the nervous plexus in the *ileum* and *colon* seemed to be normal.

Sections prepared from the *basal ganglia of the brain* showed many small perivascular hemorrhages. The bloodvessels were hyperemic and there was a moderate increase in the number of small glia cells around some of the smaller vessels. The *cerebellum* was normal.

The *skeletal muscle* removed from the abdominal wall contained an interstitial, lymphocytic infiltration which was diffuse and marked. A small, ovoid cyst filled by the sectioned parts of a trichina was found in the interstitial tissue, where it was surrounded by a dense lymphocytic accumulation.

The *femur* contained normal fat marrow throughout in which were scattered a few small foci of myeloid tissue. A rib and two vertebrae contained normal myeloid marrow except that a slight increase of nucleated erythrocytes seemed to exist.

**PATHOLOGICAL DIAGNOSIS:** Hemorrhagic colitis; nephrosis with calcifications of the tubular epithelium and tubular and vascular elastic membranes; fatty degeneration and passive congestion of the liver, passive congestion of the spleen and lungs; multiple perivascular hemorrhages of the brain; chronic myocarditis and myositis due to trichinosis.



**Comment.** The toxic action of ethylene dichlorid was already reported on by the early investigators of this substance.<sup>18</sup> Eulenberg, in 1876, anesthetized rabbits with it and found that it caused dizziness, mydriasis, complete insensibility of the cornea and hyperemia of the conjunctiva. The committee of the British Medical Association<sup>13</sup> noted convulsive movements that persisted until death in the rabbits anesthetized with ethylene dichlorid (1879). DuBois and Roux,<sup>4</sup> in 1887, DuBois,<sup>7</sup> in 1888, Parnas,<sup>8</sup> in 1888, Faravelli,<sup>14</sup> in 1892, Erdmann,<sup>17</sup> in 1912, Bullo<sup>9</sup> in 1896, and Steindorff,<sup>1</sup> in 1922, observed during the course of extensive experimentation with ethylene dichlorid that this substance, when inhaled or injected subcutaneously or intravenously, caused a temporary, white, blue-white opacity of the cornea in various animals. These opacities, they found, cleared up from the periphery after several months and were due to an infiltration of the cornea by lymphocytes and connective tissue cells. It may be mentioned in this connection that ethylene dichlorid is the only saturated chlorin compound of the ethane series that has this action. Among the unsaturated compounds that have a similar effect in dichlorethylene. The acute effect of ethylene dichlorid on the eye is a maximal dilatation of the pupil which may change after some time to myosis and anisocoria. Joachimoglu<sup>15</sup> found that ethylene dichlorid has about the same anesthetizing effect as chloroform, but that its hemolytic action is only half as strong as that of the latter substance. Kiessling<sup>16</sup> studied the action of this and related halogen compounds on the isolated frog's heart.

Kistler and Luckhardt,<sup>10</sup> who recently investigated the pharmacologic action of this substance, introduced into dogs ethylene dichlorid either by stomach tube or by intravenous injection. In general, dogs that did not die of the immediate effects (drop in blood pressure, excitement, incoördination, salivation followed by drowsiness, vomiting and dyspnea) of the drug passed through a stage characterized by depression, general sickness, emaciation, anorexia, lack of thirst, dyspnea, tarry stools and corneal opacities lasting several weeks, before they gradually recovered. The post-mortem findings typical of all dogs that died from the effect of the poisoning were as follows: Delay of *rigor mortis* by several hours, bloody discharge from mouth and nostrils, edema of the lung, subserous hemorrhages of the heart, hyperemia of the liver, brownish discolorization of the liquid blood, hemorrhages into the mesentery and intestinal lumen, albumin and bile pigments in the urine.

Sayres, Yant, Waite and Patty,<sup>6</sup> who exposed guinea pigs to the vapors of ethylene dichlorid, noted similar symptoms and post-mortem findings (irritation of eye and nose, vertigo, static and motor ataxia, retching movements, unconsciousness, incoördination

of extremities, first increased and later slowed and shallow respiration with low concentration and rapid and jerky breathing of dyspneic type with higher concentrations).

Ploetz<sup>11</sup> stated that ethylene dichlorid had a hemolytic effect and Plagge<sup>12</sup> noted that this substance inhibited fermentation of yeast.

Many of the clinical and pathologic manifestations seen in the experimental animals were paralleled in this case. The outstanding symptomatic similarities were mydriasis, dizziness, increasing stupor and the gradually progressive circulatory failure which was manifested by cyanosis, rapid pulse and unsatisfactory response to glucose, adrenalin, oxygen and atropin.

The appearance of large amounts of albumin and sugar in the urine and the occurrence of extensive tubular necrosis with calcifications resembling those seen in mercury dichlorid poisoning indicated that the kidney is the excretory organ of this substance or its decomposition product which is presumably oxalic acid. The hemorrhagic condition of the mucosa of the colon, on the other hand, was most likely the result of the toxic action of ethylene dichlorid exerted upon the intestinal mucosa during the process of absorption. It can be justly assumed that under the conditions present in this case the ingested liquid reached this part of the alimentary tract without any great delay and left for these reasons no marked injurious effects upon the upper portions of the digestive system. This observation may possibly be of some value in the future therapeutic management of cases of this type, because it suggests that high colonic irrigations given early enough and in sufficient amounts may help to remove mechanically the ingested toxic material before it can be absorbed and cause irreparable organic damage. The histologic changes existing in the brain accounted to a certain extent for the nervous symptoms observed.

In the absence of any marked myocardial lesion the actual direct cause of death was apparently a "hemorrhage" into the dilated capillary system of the internal organs resulting in circulatory failure.

**Summary.** Ethylene dichlorid, known since 1795 and first used as an anesthetic, has recently come into widespread, commercial use as a solvent and cleaning fluid.

A patient who drank 2 ounces of this liquid died within 22 hours. Stupor, vomiting, diarrhea, cyanosis and subnormal temperature were the outstanding clinical symptoms. Death was apparently caused by circulatory failure.

The ingested substance caused an extensive hemorrhagic colitis, nephrosis with marked tubular calcifications and a generalized passive congestion of the internal organs beside multiple perivascular hemorrhages in the region of the cerebral basal ganglions.

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## SPINDLE CELL SARCOMA OF THE PANCREAS.

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SARCOMA of the pancreas is very rare. Gruber could not find one sarcoma among 20,302 autopsies. In the older literature there is a report by Remo Segré who mentions among 11,492 postmortem

examinations 132 neoplasms of the pancreas, 2 of them classified as sarcomata.

Although the number of sarcomata of the pancreas given in the literature is very small, the larger part of them cannot stand criticism and should not be quoted as sarcomata.

Three different types are described: Round cell, giant cell, and spindle cell sarcoma. Marxer, analyzing these three forms in a thorough and lucid study, found that the small number of sarcomata of the pancreas should be reduced still further. He was able to prove that many of the reported pancreas sarcomata are either lymphosarcomata or metastatic tumors or not true blastomata at all, but of inflammatory origin. Some of the old cases could not be considered because they have no microscopic findings.

Among the so-called round cell sarcomata he finds lymphosarcomata, aleukemic leukemia and lymphogranuloma. It is interesting that the case of Litten which is quoted in so many papers as the first described sarcoma of the pancreas is really a lymphosarcoma. In Halasz' case Marxer is able to rule out pancreatic sarcoma, pointing out the diffuse infiltration of the mesenteric and periportal lymph nodes, and two nodular tumors in the hilus of the lung and in the mediastinum.

No blood findings are given. The diffuse infiltration speaks decidedly for a generalized lymphosarcomatosis. In fact, Marxer concludes that the existence of round cell sarcoma of the pancreas has still to be proved. The same is true of the giant cell sarcoma. The giant cell sarcoma described by Weil is apparently a lymphogranuloma and not a sarcoma.

Thus the spindle cell sarcoma is the only type that can stand criticism. Following is a short review of the cases of spindle cell sarcoma of the pancreas.

Briggs first described spindle cell sarcoma of the pancreas (1890) and Neve next (1891). Schuele first called attention in his report of a spindle cell sarcoma to the pseudocystic structure of his tumor.

In 1901 Boyd described a cystic spindle cell sarcoma with profound cachexia but no metastasis. Malcolm (1902) found a fibrosarcoma of the pancreas in a child 4 years old.

In the same year Oleari published a case with thrombosis of the portal vein and infiltration of the parenchyma of the liver.

In 1903 Ehrlich described 2 tumors of the pancreas, one an endothelioma and the other a spindle cell sarcoma weighing 3000 grams. Both were cystic. Sobolew's 4 cases (1910) illustrate the difficulty of distinguishing between primary and secondary growths of the pancreas. Two of his cases are definitely metastatic, 1 arising from a myosarcoma of the uterus. One is probably metastatic and the last is a true spindle cell sarcoma of the pancreas.

In 1912 Costantini described a primary spindle cell sarcoma of

the tail and body of the pancreas. Metastases in the liver were present.

In 1921 Lockwood described a spindle cell sarcoma of the pancreas and in 1925 Marxer a unilocular cyst with nodular wall and intensely thickened base, which microscopically proved to be a spindle cell sarcoma.

In 1930 Tschernpina described a pleomorphic sarcoma of the pancreas head combined with an intense sclerosis of the body and the tail and with cirrhosis of the liver.

In this report a case of spindle cell sarcoma of the pancreas will be described.

**Case Report.** The patient (studied clinically by Dr. R. W. Blumenthal) was a male, aged 57, married, and by occupation a butcher. His wife and 1 child were living and well, 1 child dying at the age of 10. There were no other children. His father is in good health, aged 84, while his mother died at 78. Three brothers and 1 sister are living and well. There is no other history of heart, or kidney disease, diabetes, cancer, or insanity in the family.

He was admitted to the hospital for the first time in March, 1932, after several years of slowly progressing weakness. Six months previously he had had a severe chill followed by fever and vomiting which recurred at irregular intervals over the next 3 months and was associated with moderate loss of weight. During the next 3 months he felt relatively well, however, gained 30 pounds and was able to return to light work. Immediately preceding his admission to the hospital he had again had fever, chills and vomiting.

*Physical examination* at the time revealed a patient who did not appear to be in acute pain. His remaining teeth were in poor condition. The eyes reacted normally; the lungs were apparently normal. The heart was slightly enlarged with a soft mitral murmur. The pulse was small and slow, the vessels were beaded.

The rounded abdomen showed a small umbilical hernia, no masses or tender areas. The liver border was 1 cm. below the costal margin. The spleen was not palpable. Reflexes, rectal and prostate examinations were negative.

*Laboratory findings:* Basal metabolic rate plus 20%; blood Wassermann, Kahn and Widal tests negative; blood culture, no growth; blood sugar, 196 mg. per 100 cc. of blood, non-protein nitrogen 38.7 mg. per 100 cc. of blood; creatinin 1.2 mg. per 100 cc. of blood; blood in feces, benzidine test for positive, guaiac and Rolland tests negative; electrocardiogram showed slight evidence of coronary sclerosis; red blood count 5,650,000; white blood count 18,300. On the patient's second admission (May 12) urobilinogen was found in the urine (diluted 1 to 8). Five days later it was negative; then became positive again—after 3 days (immediately after operation) it was 1 to 2. From this time on the urobilinogen increased gradually—May 24, 1 to 3; 25th, 1 to 30; 26th, 1 to 75; 27th and 28th, 1 to 50; 31st, 1 to 80; June 1st, 1 to 100. Then it came down to 1 to 40 until he died June 4th. There was always bile pigment in the urine.

His highest temperature while in the hospital was 104° F., the highest pulse rate 108, respiration 22. The urinary sugar ranged from 4+ to negative. He was discharged from the hospital April 18, 1932, as improved, with a probable diagnosis of subacute bacterial endocarditis and diabetes mellitus.

After a few days at home he was forced to go to bed on account of fever

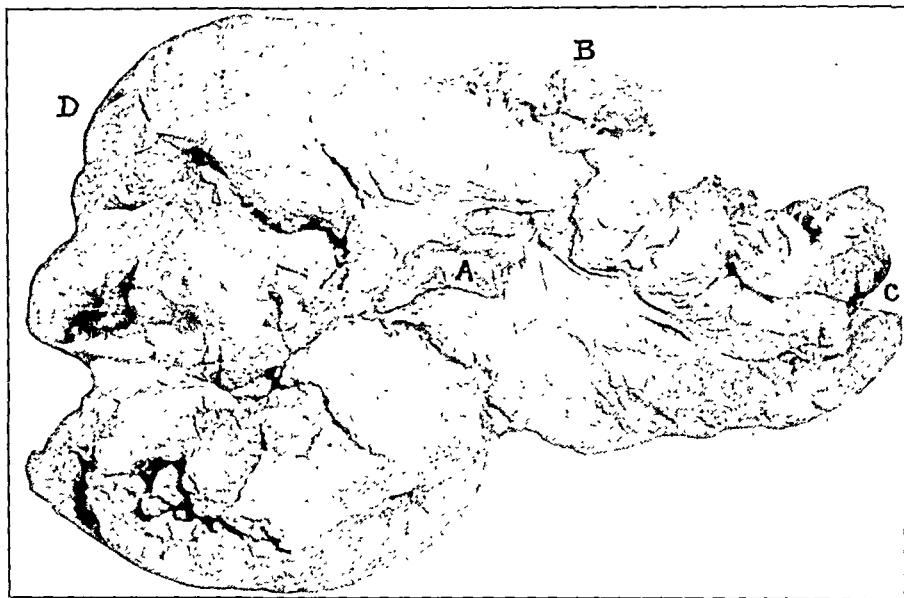


FIG. 1.—Gross view of incised pancreas. *A*, Thrombus; *B*, body; *C*, tail; *D*, head.

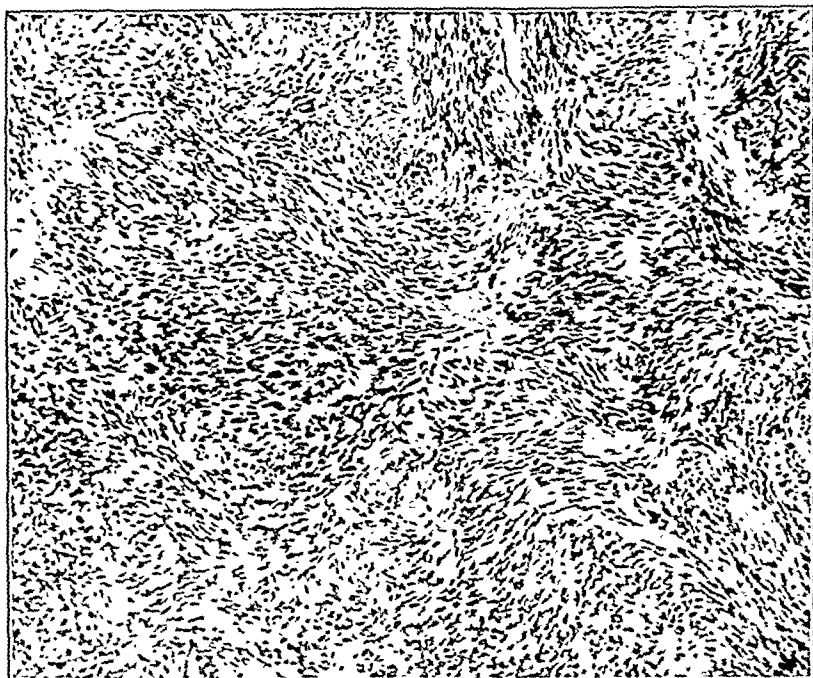


FIG. 2.—Microscopic section: sarcoma of pancreas, low power.

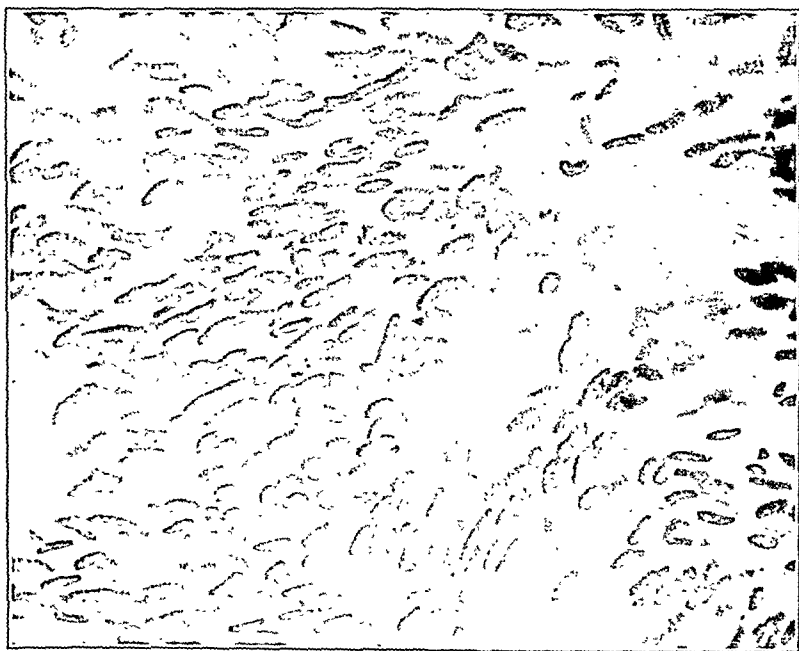


FIG. 3.—Microscopic section: the same high power.

and weakness. He had had no pains or chills. Usually he felt well in the morning but by evening the fever and sweating would begin. There had been considerable loss of weight as well as a moderate jaundice.

He entered the hospital a second time on May 12, when his blood pressure was 110 systolic and 64 diastolic, his nutrition poor, and he was apparently very sick. The history of jaundice, anorexia, loss of weight, with physical findings of tenderness in the gall bladder region, together with a mass in the right subcostal area, suggested cholecystitis with adjacent pancreatitis (possibly malignant) and hepatitis. A Roentgen ray examination of the gall bladder with dye revealed a normally functioning gall bladder, which was pushed laterally and deformed by a tumor in the midabdomen. The entire duodenum was displaced laterally in half a circle, probably by tumor originating in the pancreas.

An *exploratory operation* (May 20) revealed an enormously distended, thin-walled gall bladder, as with a carcinoma of the pancreas or a stone in the ampulla. The pancreas was the size of two fists but not nodular. The liver was large with rounded edges and irregular areas. After the exploratory operation he ran a stormy course and died June 5, 1932.

**POSTMORTEM EXAMINATION** (by Dr. E. J. Oesterlin 3 hours after death):  
*Anatomic Diagnosis.* Pleomorphic spindle cell sarcoma of the pancreas.

The head of the *pancreas* was enlarged to the size of a large grapefruit and contained many cystic cavities, without apparent epithelial lining. The entire parenchyma of the pancreas was replaced by a coarse fibrous tissue. Microscopically, the tissue consisted partly of mature coarse connective tissue fibers and partly of irregular whorls of pleomorphic cells, among which spindle shaped cells predominated. Occasional giant cells were found. Scattered through the tumor were necrotic areas, invaded by neutrophils. The margins of the cystlike spaces was also invaded by neutrophils. The body and tail of the pancreas showed marked fibrosis.

The *spleen* was much enlarged, weighing 370 gm. The pulp was easily scraped from the cut surface.

Acute splenitis.

The *liver* was considerably enlarged, weighing 2130 gm. It contains multiple abscesses, frequently fused, varying in size up to 4 cm. in diameter. Culture of the pus showed *B. coli*.

*Microscopic examination* showed many necrotic areas invaded by neutrophils, with adjacent granulation tissue. There were also chronic changes present: the periportal connective tissue and the bile ducts were much increased. The liver cells showed fatty degeneration.

Multiple abscesses in cirrhotic liver.

Thus there were parallel acute and chronic processes in both the pancreas and liver. The acute process consists in the inflammatory cyst formation of the pancreas and in the liver abscesses; the chronic process in the fibrosis of the pancreas and the cirrhosis of the liver.

It seems probable that the sarcoma of the head of the pancreas was developed on a preëxisting fibrosis. The fact that there was still much mature connective tissue remaining in the head of the pancreas points distinctly in this direction.

Boyd, Constantini and Tscherpnina also report fibrosis of the pancreas in their cases.

**Summary.** 1. A spindle cell sarcoma in the head of the pancreas has been described.

2. The sarcoma was combined with a marked fibrosis of the body



and tail of the pancreas and with cirrhosis of the liver with multiple abscesses.

3. The possibility of a causative relation between the fibrosis of the pancreas and the sarcoma has been stressed.

4. A review of the definite spindle cell sarcomata in the literature is given.

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#### CONGENITAL CYSTS OF THE LUNG.\*

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In 1925 Koontz<sup>1</sup> collected and examined 108 cases of congenital cysts of the lung, of which 43 were in children, and, as he notes,

\* Read before the Philadelphia Pediatric Society, June 14, 1932.

none reported in American articles. Further perusal of the literature adds a rather limited number of cases, some of which appear in American journals. In view of the paucity of articles upon this subject, and in view of the rapidly expansile nature of the lesions observed, the authors feel that the following case merits reporting.

**Case Abstract.** C. W., aged 4 months, colored, was admitted to the Children's Hospital of Philadelphia, November 9, 1931. His father was 45 years old and was said to be well. His mother was 39 years old, said she was well, and had had no miscarriages, but had given birth to 11 children, of whom 10 were living. One boy had died at 1 year of pneumonia. There was no history of syphilis or tuberculosis in the family.

The patient was born by a normal delivery at full term and weighed 9 pounds. His newborn period was without symptom or difficulty. He was breast fed for 3 weeks and then fed upon a suitable and adequate cow's milk formula, upon which he developed well. He was given orange juice and cod-liver oil in proper amounts.

The child's illness began 2 weeks before admission with coryza and cough. He did not seem very ill until 1 week had passed, when he developed a high fever, cough and rapid, grunting respiration. His sleep was disturbed, but he took his formula well. He vomited a little with his cough, and had 6 to 8 green, watery stools a day. There were no convulsions.

At the time of admission the physical examination showed the following: A well developed child, breathing regularly but rapidly, restless, and with some retraction of the head. The skin was dehydrated. The fontanelle was small and full. No craniotabes was present. The left ear drum was red and full; there was some mucous secretion in the nares. The lips were dry and the tongue somewhat coated. No teeth were erupted. The tonsils were normal in size but were reddened, as was the postpharyngeal wall. The eyes were normal. There were no enlarged glands present. The chest was of normal girth and contour and showed slight beading of the ribs. There was dullness over the left upper lobe with bronchial breathing and many crackling râles in the left axilla. The liver was palpable in the normal position for the age. The epiphyses were slightly enlarged. The reflexes were normal.

A diagnosis of left upper lobar pneumonia was made. Immediate steps were taken to combat the dehydration and prostration. A transfusion of 50 cc. of citrated blood was given, followed the next day by a hypodermoclysis of 150 cc. of saline. After several days, signs of consolidation were noted in the right upper lobe. A diagnosis of migratory pneumonia was made, and another transfusion of 35 cc. was given. After about 3 weeks the temperature descended rather gradually into a normal zone, where it stayed for 3 weeks more. During the first 3 weeks otitis media was present and both ears were opened upon a number of occasions. During the period of acute illness, the child at first gained weight; but later, due to anorexia and vomiting, this gain was lost. After the temperature became normal, the child began to gain again. In spite of this normal temperature and gain of weight, there was no appreciable clinical improvement so far as lung findings were concerned. About 6 weeks after admission the temperature began to rise again, but during this rise the child seemed to be making a gain of strength, and even gained some weight. However, after about 2 weeks of fever, attacks of weakness and cyanosis came on, and in one of these attacks, on January 18, 1932, the infant died.

**Laboratory Findings.** Urines were normal save for traces of albumin; the Wassermann and Kahn tests and blood culture were negative. Mantoux tests with ascending doses of old tuberculin were all negative. The blood

at the time of admission showed a secondary anemia, 39% hemoglobin, 2,150,000 erythrocytes, 12,500 leukocytes, 91% of which were neutrophils. After treatment with transfusions and iron medication, in 1 month this rose to 70% hemoglobin and 3,920,000 erythrocytes. This latter figure was not due to anhydremia.

At first, our impression was that of a migratory type of lobar pneumonia with delay of resolution, due perhaps to the severity of the secondary anemia. A further thought was that the delay was due to an underlying tuberculous infection. The negative family history, the persistently negative tuberculin reaction, the absence of tubercle bacilli in the gastric contents, made it impossible to confirm this diagnosis, yet its possibility was not entirely excluded. Still later a diagnosis of abscess of the lung was considered, and this likewise could neither be confirmed nor rejected positively.

*Roentgenologic Findings.* The findings made by Dr. R. S. Bromer in a series of films, a number of which are reproduced here, may be summarized as follows:

At the time of admission, films showed a bilateral consolidation. It was suspected that the lesions were tuberculous and that fluid was present between the upper and lower lobes of the left lung. A week later (Fig. 1) the right upper lobe was much clearer and the appearances suggestive of cavity were gone. It was believed that these had been caused by an emphysematous bleb. The left upper lobe was denser than before, and a ringlike shadow had appeared below it. This was also believed to be due to an emphysematous bleb. Two weeks after admission the left upper lobe was less dense, but two ringlike shadows were seen.

Five weeks after admission a film showed at the left base a large, round, ringlike shadow, also a number of smaller ones in the left upper lobe. Six weeks after admission films showed a return of the density in left upper lobe and showed the ringlike shadow still present. Seven weeks after admission the large ring shadow was thought to resemble an abscess cavity or possibly a pneumothorax.

Eight weeks after admission multiple large, circular shadows were found in the left upper lobe; the ring shadow in left lower lobe had decreased in size. It was thought that because they were so large that they could not be due to emphysematous blebs, but might be due to abscess cavities. It was argued, however, that if they were abscess cavities, they should not almost disappear at times, and should not decrease in size.

The last film was taken 4 days before death. It showed all the cavities previously mentioned, and one in the right upper lobe. The large ring-shaped shadow in the left lower lobe was shown to displace the lower branch of the left bronchus, and for this reason pneumothorax was considered the most likely cause.

*Necropsy* (by Dr. Waltz, 2 hours after death). *Gross Description.* *Left Lung.* The upper lobe is deeply grooved across the lower anterior portion, producing almost complete separation into a middle and upper lobe.

The upper outer and posterior portion of the upper lobe is attached to the chest wall by firm, fibrous adhesions. On breaking these adhesions a large, thin-walled cavity was ruptured with an outward gush of air. This cavity occupies most of the upper lobe, is empty, and measures 4.5 by 4.5 by 4 cm. The lining is smooth, but the wall is ribbed and grooved by what appears as an interlacing of dilated or thickened bronchi. The cavity shows direct connection to one of the larger bronchi. A probe being easily passed through the bronchus along one side of the cyst wall

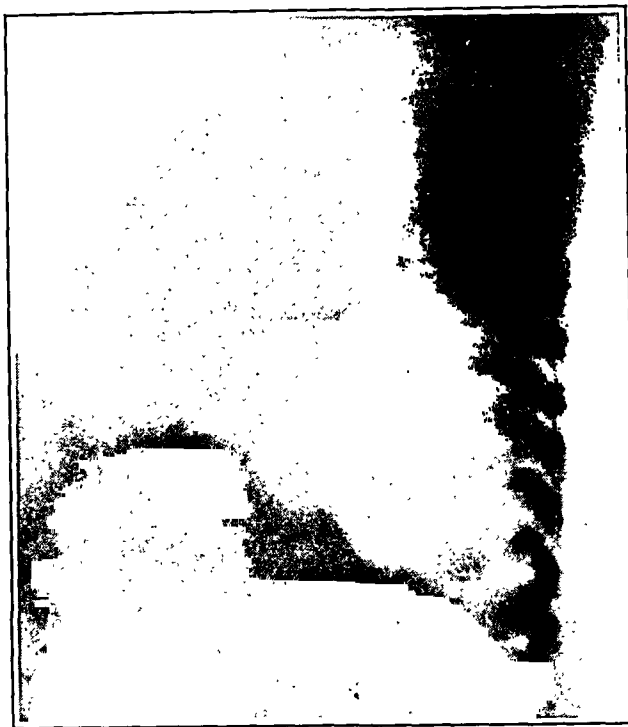


FIG. 1.—November 19, 1931. Increased density in left upper lobe with a small kidney-shaped rarefaction. A ring shadow in the upper lobe and a smaller ring shadow on the interlobar line (1.5 x 2 cm.).

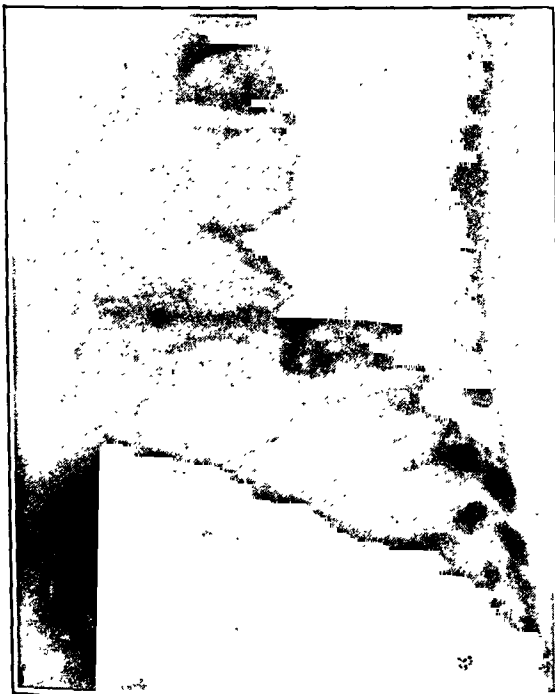


FIG. 2.—December 17, 1931. Shows lessening of density in lungs, especially over the cyst in the left upper lobe; the lower ring shadow is much larger (2.5 x 3.5 cm.).

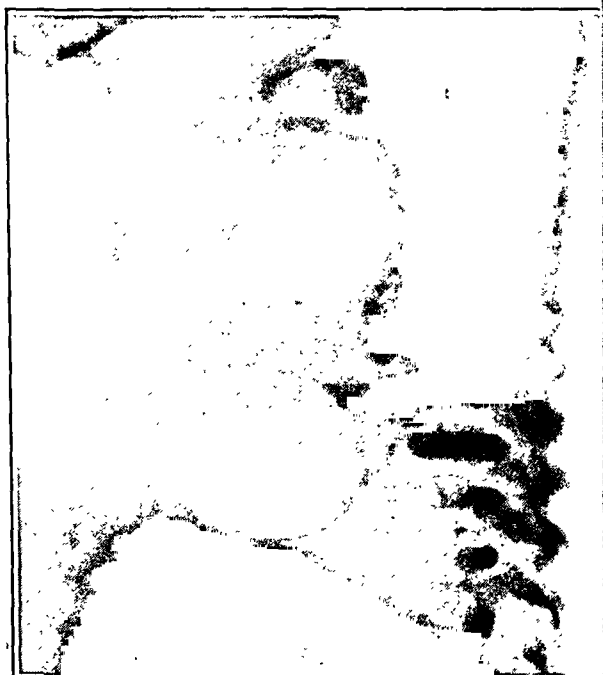


FIG. 3.—January 9, 1932. Lower ring shadow much larger (3.5 x 4.5 cm.). Upper shadow larger and has loculated appearance. Pneumonia cleared up.



FIG. 4.—January 14, 1932 (4 days before death) oblique. Shows further increase in size of interlobar ring shadow. The cavity in the upper lobe has increased enormously. Taken at the time dyspneic attacks began.

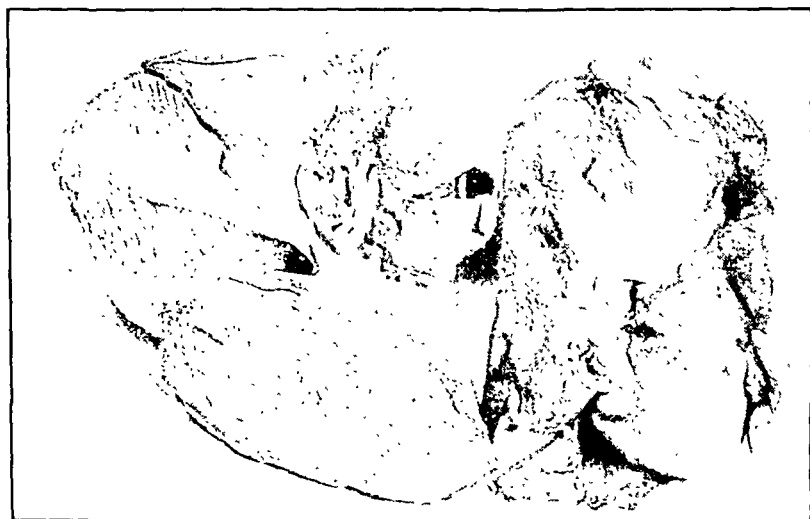


FIG. 5.—Bronchi up, left lung to right; below, large cyst in interlobar space. Upper lobe cysts under white roughened area. Right lung to left. Incision into cyst in upper lobe, walls of which are separated by a stick.

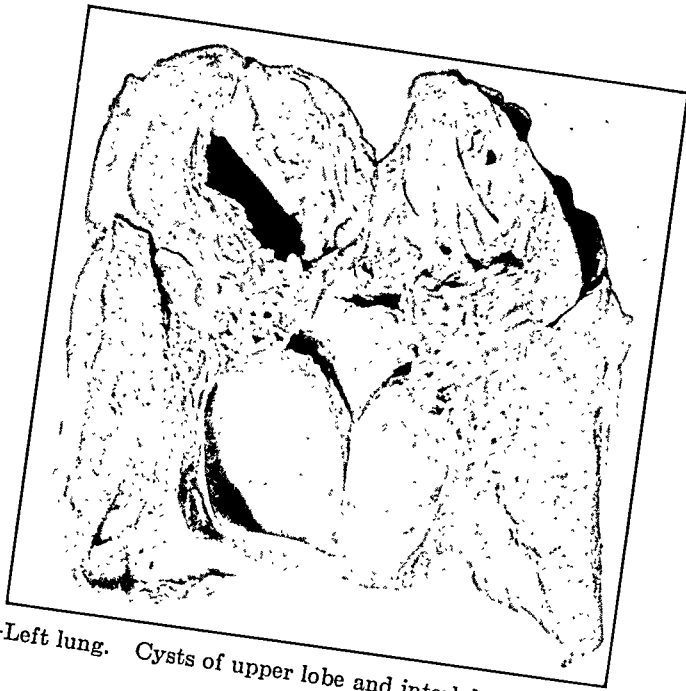


FIG. 6.—Left lung. Cysts of upper lobe and interlobar space laid open.

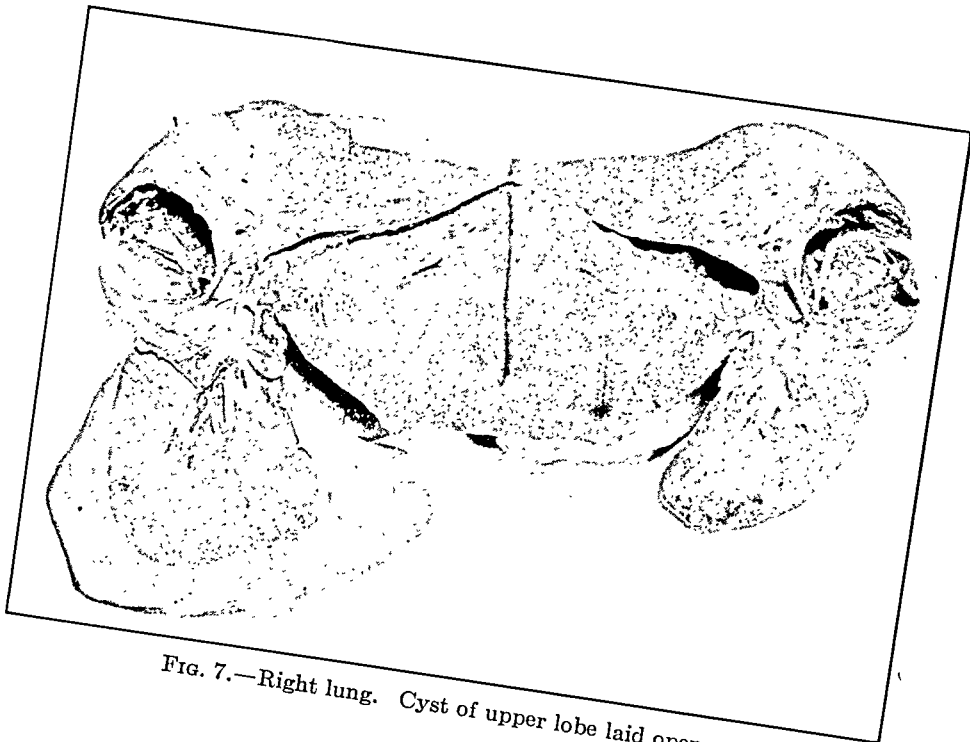


FIG. 7.—Right lung. Cyst of upper lobe laid open.



Low power (100 X).

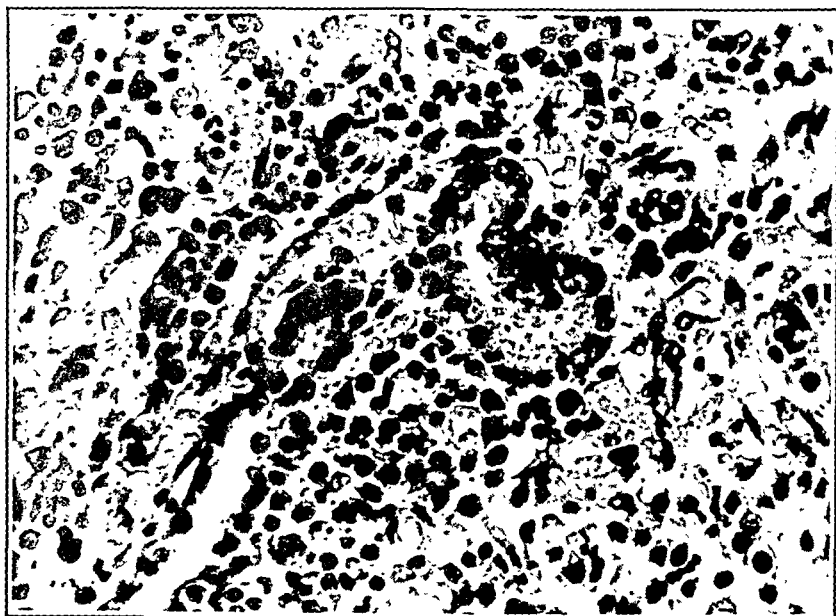


FIG. 8.—(High power 440 X.) Adenomatous or acinus-like spaces somewhat resembling rudimentary bronchi, with flattened atypical epithelium. The blood-vessels show thickened walls. The alveoli are partially collapsed and infiltrated with small round cells; the walls are thickened with fibrous connective tissue.

for 2 cm. before opening into the cyst. Pressure on the side wall from air within the cyst could easily produce a valve effect by compressing the bronchus during expiration. A small lower posterior tip of the lobe is consolidated. The upper anterior portion of the lobe shows several small cystlike cavities ranging from a few mm. to 1 cm. in diameter. These are smooth walled, some contain pus. Between these cysts the lung tissue is firm and fibrous.

The extra middle lobe is fairly crepitant throughout. There are no cysts demonstrable in this lobe.

The lower lobe is deep red in color and boggy. There are no cysts found within the lobe. However, there is a large, thin walled cyst bulging out in the interlobar fissure between the lower and middle lobe. The cyst cavity is 4 by 4 by 4 cm. and contains only air. The lower portion of the wall is apparently part of the interlobar pleura of the lower lobe. The upper portion is part of the interlobar pleura of the middle lobe, the anterior and posterior walls are apparently a continuation of these pleural coverings, and are bluish and almost transparent. This cavity was thoroughly studied for a possible opening from a bronchus, but none could be demonstrated.

*Right Lung.* The lung consists of the normal three lobes. There are firm, fibrous adhesions over a small area of the posterior part of the upper lobe; when these are freed a small air-containing cyst 1.5 cm. in diameter is elevated above the surface somewhat, but extends into the lung for the most part. Near this are two other slightly elevated areas which are about 1 cm. in diameter which, on section, appear to be made up of small honey-comblike air-containing cysts. Below these is a larger cyst 3.5 by 3.5 by 3 cm., situated in the lower part of the upper lobe posteriorly, so that the wall on the lower surface is the interlobar pleura of the upper lobe. The cyst is smooth walled, but filled with thick, creamy pus.

The middle lobe is fairly crepitant throughout. The lower lobe is of a deep red color and boggy, apparently congested and edematous; no cysts are demonstrable in this lobe.

All cysts containing pus or fluid were cultured and examined for tubercle bacilli and parasites. Cultures showed Group IV pneumococcus in all such cysts. In some cysts *Bacillus coli* was also present. No tubercle bacilli or parasites were found in any cyst.

*Microscopic Findings.* The large interlobar cyst of the right lung is covered with a thin wall of fibrous connective tissue. On part of the wall no lining epithelium can be demonstrated; in other areas it is covered with a single layer of low epithelium with fairly large nuclei; in a few places these are arranged in layers of two or three cells. The nuclei are elliptical with the long axis parallel to the cyst wall. These cells do not have the appearance of the usual columnar epithelium of the bronchi, differing in the absence of cilia, in form, and in the direction of their nuclei. They have more the appearance of a type of squamous epithelium. It suggests that they had been subjected to the stretching of the cyst wall and to the long continued pressure from the cyst contents. Subjacent to the cyst wall the alveolar tissue is partially atelectatic.

The largest cyst in the upper right lobe shows a lining similar to that just described. In the partially consolidated and partially atelectatic tissue subjacent to this cyst are found rather well developed bronchi surrounded by partially collapsed alveoli somewhat infiltrated with small round cells; the alveolar walls are markedly thickened with fibrous connective tissue. These areas show many small bloodvessels with thickened walls. Grouped about a bronchus are frequently found acinus-like spaces lined with somewhat flattened ciliated columnar epithelium.

This picture suggests a hyperplastic growth of bronchial tissue corresponding to that of Stoerk,<sup>2</sup> which he considered a tumor of embryonal



bronchial tissue. Couvelaire<sup>3</sup> also described a cystadenomatous formation in his case. The cyst in the left upper lobe is filled with pus and is largely denuded of epithelium. Surrounding this cyst is a rather thick area of fairly firm, fibrous connective tissue showing loops of new bloodvessel formation.

**Comments.** According to Eloesser,<sup>4</sup> congenital cysts may be divided into two principal classes: 1, Large solitary cysts; 2, multiple smaller cysts. The latter condition is usually spoken of as congenital cystic disease; the cysts may be few and fairly large, or they may be small and too numerous to count. In the latter circumstance, they receive the designation of "honeycomb lung."

Solitary cysts vary greatly in size. They may be large enough to occupy the space usually occupied by a whole lobe of a lung. They may be of a size which can be concealed within the lung parenchyma. Sometimes they are mere outpouchings from the trachea, esophagus, or a bronchus. They have been known to be large enough to pass through the diaphragm into the abdominal cavity.

Cystic disease, or honeycomb lung, is disposed in different ways in different cases. At times a whole lobe is diffusely involved. At times a whole lung is involved. At times only part of a lobe is affected. At times, as in this case, cysts may be found in widely separated parts of both lungs.

The cysts may communicate directly with a bronchus, but in many cases this communication is not present and the cyst cavity is isolated. In some instances the cysts appear to be dilatations of a main bronchus, and branch bronchi or secondary cysts may be found opening into them. More frequently they seem to be dilatations of small bronchioles, either communicating or non-communicating. At times a number of these closed sacculations appear to be strung upon a fibrous cord, like beads upon a thread.

Cysts are usually lined with a single layer of ciliated columnar epithelium. The cyst walls are usually smooth, usually free of ulceration and inflammatory deposits, indicating that they are not broken down abscess cavities. The lining wall, however, may become inflamed. They usually contain air, or fluid, or more often both together. The fluid is said to be very high in albumin content, and, in a number of cases, of a brownish color. It usually contains few cells, if inflammation is absent. Anspach and Wolman<sup>5</sup> suggest that the cysts originally are fluid filled and that later this fluid is extruded by coughing or other pressure, as happened in a case described by them.

In cases where the ciliated epithelium is not present, we find a lining of one or more layers of cuboidal or even flattened epithelium. There may be no lining at all, the fibrous membrana propria forming the cyst wall. External to this are frequently found concentric fibers of smooth muscle, and at times pieces of cartilage. The amount of muscle fiber and cartilage is usually too great to suggest

that it is a mere expansion of that normally present in a bronchus. It is more probably due to an actual hyperplasia. In some cases mucous glands are found in the cyst wall. In addition to inflammation of the lining wall of the cyst, inflammation of the tissues immediately surrounding the cyst is frequently found. This is usually pneumonic in type.

*Clinical Considerations.* Cases arrange themselves clinically into two main types. The first type has been termed *infantile* and is characterized by sudden attacks of dyspnea, cyanosis and collapse, in which death may occur. The other type is spoken of as the chronic form. In this form, bronchopneumonic areas are found in the cystic lung. In the case reported, both dyspneic attacks and bronchopneumonia were found. In many cases tuberculosis is suspected as in this one, but a certain confirmation of diagnosis cannot be made from Roentgen films, tuberculin tests and sputum examinations.

Pneumonia is easily identified in the presence of cysts, but very frequently the cyst causes suspicion of cavity or abscess formation. Gibson,<sup>6</sup> by introducing lipiodol, was able in his case to demonstrate the cysts and a fluid level in them by changing the posture of the patient. In the usual Roentgen ray films the cysts appear in varying density as oval or circular areas of lessened density, often surrounded by a sharply defined margin, which may be interpreted as pneumothorax and be aspirated. Clairmont<sup>7</sup> calls attention to the fact that an interlobar line often may be seen crossing a cyst, but not a pneumothorax. Cysts, unless very large do not give any very definite physical signs, but the pneumonia which surrounds them indicates itself in the usual manner.

Treatment of the cysts is not very satisfactory. Inasmuch as 35 of Koontz's collected cases lived 30 years or more, and 1 to the age of 84, it may be accepted that the condition is not always fatal at an early age. Operation has been attempted in a number of instances. Clairmont operated upon a boy of 10, removing a cystic middle lobe, but the patient died of postoperative shock. Sauerbruch<sup>8</sup> resected cystic lobes in 4 adult cases diagnosed empyema, all of whom recovered. R. T. Miller<sup>9</sup> reports a patient of 5 weeks into whose cyst was inserted a one-way air valve; this patient lived comfortably for several months, but then suddenly died. From these observations it may be concluded that cystic disease is of graver import in early life and that operative procedures at this age are at the present time of considerable danger.

*Comment.* The English authors have attributed the cysts to bronchopneumonia and atelectasis occurring after birth. The progressive increase in the size of the cavities demonstrated roentgenographically in this case indicates that changes were continuing during the period during which it was under observation. In several of the cavities direct communication with a bronchus could be demon-

strated. In the cavities in the left upper lobe this communication was found at necropsy, but could not be found after hardening in formalin. In the large cyst between the left lower lobe and the anomalous left middle lobe formation no communication could be found at any time. In fact, this cyst was immersed beneath the surface of formalin for 1 year without the slightest deflation or loss of air content. It is to be presumed that its communication was by means of a very narrow channel, allowing the access but not the egress of air. deLange<sup>10</sup> has postulated three methods of origin of these cysts:

1. A fetal bronchial inflammation with valvelike stenosis of the bronchioles. This she believes to be almost invariably syphilitic.

2. A hyperplastic condition in which an excess of tissue occurs. In some of the cases in this category there is found bronchial overgrowth and cystadenomatous formation difficult to attribute to mere bronchial dilatation.

3. A hypoplastic condition in which the alveolar tissues have failed to develop and in which bronchial enlargement has taken place in compensation therefor.

We believe the cysts in our case are of congenital origin because of their smooth lining wall and because of the presence of a flattened atypical lining epithelium. The presence of an anomalous lobe lends support to this view. Furthermore, the presence of certain acinus-like formations seen in one of the sections indicates an element of hyperplasia of tissue, which we believe to be a defect in embryonal development. In addition to this factor, we believe that a mechanical factor, gradual inflation of the cyst has been operative since respiration began.

**Summary.** A case of congenital cystic disease of the lung in an infant of 4 months is presented, with roentgenographic studies and necropsy findings. Progressive enlargement of the cysts is visualized in serial films. Microscopic findings suggestive of abnormal embryonic development are described.

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**FACTORS AFFECTING THE APPEARANCE AND DURATION OF GLYCOSURIA.\***

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THE present work is an attempt to correlate the blood sugar level with the appearance and disappearance of glycosuria and to study the factors which control the excretion of sugar in the urine. An intravenous tolerance test was used in which an amount of glucose just sufficient to produce glycosuria was injected. In order to correlate accurately the blood sugar level with the time of appearance and disappearance of glycosuria, capillary blood specimens were collected at frequent intervals and simultaneously urine specimens were obtained by catheter which was kept in the bladder throughout the experiment. Only women subjects have been studied because of the ease of catheterization.

**Procedure.** Our procedure was as follows: After an all-night fast a catheter was placed in the bladder with sterile technique. A preliminary blood specimen was collected and the bladder emptied. Glucose in 50% solution was injected rapidly into the arm vein, usually during 30 to 60 seconds. Urine samples were collected from the catheter at minute intervals for the first 15 minutes and later at somewhat longer intervals, while capillary blood samples were collected from the ear at 1- to 3-minute intervals for 6 minutes and then at 6-minute intervals until the end of the experiment. Qualitative tests for sugar in urine were run in every case to assure the continuance of the experiment until after the disappearance of glycosuria and in most cases the sugar excretion was determined quantitatively. Blood sugar analyses were done by the micromethod of Folin as modified by Folin and Malmros,<sup>8</sup> and the urine specimens were analyzed by Benedict's qualitative and quantitative methods.<sup>7</sup>

Ten grams of glucose were given in most of the tests as it was found that this amount could be relied upon to produce a glycosuria of moderate duration. The figure was arrived at from preliminary experiments, using doses varying between 3 and 8.8 gm., which frequently failed to produce glycosuria at all, and doses of 12 to 20 gm., which produced greater hyperglycemia and prolonged glycosuria.

The results of the analysis of blood and urine were plotted and the blood sugar values at which glycosuria appeared and disappeared were determined

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by interpolation. For instance, in Patient "ST" the urine collected in the fourth minute after injection was positive for sugar. The corresponding point on the blood sugar curve was 148 mg. per 100 cc. The urine specimens continued to be positive for sugar for 25 minutes, while the specimens collected at 29 minutes and thereafter were negative. The blood sugar concentration at 29 minutes by interpolation from the curve was 101 mg. per 100 cc.

Thirty series of observations were carried out on patients in the Vanderbilt University Hospital who had no known abnormality in carbohydrate metabolism or renal function. In each case a similar type of curve of blood sugar concentration was obtained. The first specimen, taken from 1 to 3 minutes after injection was completed, showed a maximum value from which the concentration rapidly fell. The blood sugar values found before injection were all in the normal range. Such variations as occurred within this range showed no relation to subsequent values and hence are omitted from the table. While it is true that urine is formed from plasma and our results were obtained with whole blood, the equilibrium between cells and plasma is established with such rapidity that only in the first sample of blood taken after injection could this element of uncertainty be noticeable. To have carried out the analyses on plasma would have necessitated sacrifices in other more important factors in the experiments.

**Appearance Time of Glycosuria.** When glucose is administered by mouth there appears to be a definite delay in its appearance in the urine which may amount to over one-half hour. This phenomenon after orally administered glucose has been called, perhaps inaccurately, the renal lag, and while noted by earlier observers was first emphasized by Faber and Hansen.<sup>1</sup> During this interval preceding glycosuria the peak of the blood sugar values is usually passed and the hyperglycemia begins to wane. The reason for this is not known, but in the words of Faber and Hansen, "It seems to be an expression of the effort of the kidneys to avoid the excretion of sugar as far as possible."

When an adequate dose of glucose is administered intravenously it appears in the urine very quickly, partly perhaps because some of it is carried directly to the kidney without first going to the liver as does ingested glucose. In our series of 30 cases, glycosuria set in in 5 minutes or less in 14 cases. The renal lag was consequently very small and was partly accounted for by the time required to fill the ureters, bladder and catheter. Nevertheless, it seems that even with intravenously administered sugar a definite interval of time over and above that necessary for simple excretion as determined with non-threshold substances elapses between the presentation of a quantity of sugar to the kidney and its appearance in the urine. Furthermore, frequently this excretion does not start until the blood sugar values are decreasing.

TABLE 1.—THRESHOLD VALUES AND RENAL LAG.

Patient.	Fluid, cc.	Glucose given, gm.	Glucose excreted in urine, gm.	Injection time, sec.	Glycosuria.			Urine.		Blood sugar level (per 100 cc. capillary blood)			
					Appearance, min.	Disappearance, min.	Duration, min.	Vol., cc.	Rate.*	Peak, mg.	Accuracy.	Appearance, mg.	Disappearance, mg.
St. . .	..	10.0	0.31	28	4	29	25	56	1.3	150	—	148	101
Car. . .	..	10.0	0.12	22	11	25	14	183	5.2	162	+	123	102
Wi. . .	..	10.0	0.09	50	5	25	20	108	2.7	179	—	159	110
Pr.I. . .	..	10.0	0.12	54	7	>48	>41	25	0.5	169	+	168	100†
Pr.II. . .	1000	10.0	0.15	37	4	9	5	310	10.3	173	—	168	152
Du.‡ . .	..	10.0	0.09	50	5	33	28	311	5.1	131	—	121	82
Ha.I. . .	..	5.0	0.00	20	..	..	..	64	1.7	152	—	..	..
Ha.II. . .	..	7.5	0.01	30	8	15	7	138	2.8	160	+	138	109
Ha.III. . .	..	10.0	0.06	45	5	32	27	75	1.6	198	—	193	139
Jo. . .	..	10.0	0.10	77	4	16	12	109	2.6	246	+	204	168
Ba. . .	..	20.0	1.36	240	< 4	25	>25	226	2.7	494	—	494	324
Ham.I. . .	..	3.0	0.00	30	..	..	..	27	0.7	134	—	..	..
Ham.II. . .	..	12.0	0.13	60	5	26	21	108	1.4	398	+	330	162
Gr. . .	..	10.0	0.20	60	6	21	15	152	1.1	304	+	230	182
Br. . .	..	12.0	0.20	60	< 8	25	>15	42	0.8	220	+	204	139
Ral. . .	..	10.0	0.13	42	15	51	36	103	1.7	196	+	154	125
La.I. . .	..	10.0	0.13	35	4	29	25	57	1.3	177	+	155	120
La.II. . .	1000	10.0	0.15	30	4	9	5	111	4.6	219	+	170	150
La.III. . .	1000	10.0	0.16	34	3	12	9	74	2.9	194	—	181	150
Hi.I. . .	..	7.5	0.00	22	..	..	..	71	2.4	147	—	..	..
Hi.II. . .	<i>ad lib.</i>	10.0	0 10	45	4	13	9	102	2.8	176	—	172	154
Hi.III. . .	<i>ad lib.</i>	8.8	0.07	40	13	17	4	15	0.5	200	+	172	158
Hi.IV. . .	<i>ad lib.</i>	10.0	0 15	34	6	17	11	78	2.4	209	+	188	170
Be. . .	..	6.0	0.00	25	..	..	..	21	0.8	138	—	..	..
Se. . .	..	10.0	0.00	31	..	..	..	89	3 7	172	—	..	..
Cu. . .	..	10.0	..	60	4	>48	>44	40	0.8	304	—	294	..
Can.I. . .	..	8.0	..	90	32	>44	>12	24	0.5	210	+	139	..
Can.II. . .	..	12.0	..	120	<14	>38	>24	32	1.3	290	+	189	..
Bo.I. . .	1000	10.0	0.00	60	..	..	..	402	21.2	252	—	..	..
Bo.II. . .	..	10.0	0.21	40	4	29	25	75	2.2	252	+	226	159

\* Cc. per minute.

† Blood sugar concentration at 48 minutes.

‡ This patient was suffering from general paresis and a variety of other things so that any anomalies in the results must be discounted because of her extremely poor state of health.

With our standard dose of 10 gm. of glucose the renal lag equalled or exceeded 7 minutes in 3 experiments. The phenomenon is, however, influenced by constitutional and other factors. Thus occasional values much in excess of this are found even when smaller doses of glucose are used. As may be seen from Table 1, a lag of 32 minutes occurred in Patient "Can." after a dose of only 8 gm. This patient was interesting because when the dose was increased to 12 gm. the beginning of excretion was still delayed for

almost 14 minutes. Apparently this was a personal trait. In the case of another patient (Hi.III), a delay of 13 minutes may have been due to an almost complete anuria.

Previous investigators have called attention to the fact that glycosuria frequently does not set in until after the maximum blood sugar level has been passed.<sup>1,9</sup> Our experience agrees with this finding. While the peak was always passed in our experiments using the intravenous method, sugar did appear in the urine while the blood sugar values were rising in some (unreported) experiments in which sugar was given diabetics by mouth. An examination of the results of other observers as presented in the literature reveals a similar lack of uniformity. There appears to be no relationship between the attainment of the maximum hyperglycemic level and the appearance of glycosuria. That glycosuria can play but little part in the reduction of the hyperglycemia is evident from the figures in Table 1, showing the actual amount of sugar that escaped in the urine in several of our cases. The maximum amount recovered was 7%.

**The Appearance Level of Glycosuria.** The term threshold is usually defined as the concentration of sugar in the blood at which glucose appears in the urine in quantities sufficient to respond to the usual tests. It should be clearly understood, however, that this definition refers to the *minimum* concentration at which sugar *can be made* to appear by the administration of carbohydrate. In experiments of our own and of others<sup>9</sup> glycosuria was made to appear in normal people at much higher levels. In fact, it seems to be possible to produce it at almost any level above the true threshold, by the injection into normal people of large enough doses of glucose and in diabetics by its oral administration. Thus in 1 of our patients 20 gm. of glucose gave an appearance level of 494 mg.% and this was probably submaximal. It is obviously not the true threshold. In another case a 12-gm. dose gave an appearance level of 189 mg.%, but 8 gm. of glucose resulted in glycosuria only at 139 mg.%.

For determining the true threshold, Faber's scheme<sup>1</sup> of using two doses of glucose, one of which just fails to produce glycosuria and another slightly larger dose which results in a brief excretion of sugar appears to be the more accurate one. Our values cannot be considered as thresholds in the true meaning of the term. We were interested not in determining the true threshold, but in studying the factors which alter the blood sugar concentration at which glycosuria appears.

Nevertheless, because of the size of the dose selected, the values with our standard dose fall in the range of threshold values found by previous observers; Peters and Van Slyke,<sup>6</sup> giving an approximate range of 140 to 200 mg.%.

Judging from the slopes of the curves the actual maximum values

attained by the blood sugar were probably momentary, occurring during or immediately after injection, and only by chance could they have coincided with the taking of the samples of blood. There was some slight variation in the injection rate, and from 1 to 5 minutes were required for obtaining the first blood specimen. The blood sugar maxima observed with 10 gm. of injected glucose varied considerably, ranging from 131 to 304 mg.%, and for the above reasons give no idea of the true maxima. Since the first blood sugar values were submaximal, it was not possible to calculate a value for the beginning of glycosuria if sugar was already present in the urine when the first blood sample was collected. Only when sugar appeared in the urine between two blood sugar values on the descending branch of the curve could its appearance in the urine be accurately correlated with the blood sugar level. Nine of our cases to which a dose of 10 gm. was given and 6 to which larger or smaller doses were administered showed this picture. Such samples are marked "+" in the column headed "Accuracy" in Table 1.

The blood sugar concentration at the appearance of glycosuria in those patients receiving 10 gm. of glucose varied from 123 to 230 mg.%, but in 6 of the 9 cases was between 154 and 204.

The question of the constancy of the threshold in individuals has been thoroughly discussed in the papers of Faber and Hansen,<sup>1</sup> Sakaguchi<sup>2</sup> and others. As the above authors have pointed out, much confusion has arisen from the crudeness of the methods used. Table 2 shows the results of duplicate determinations on each of

TABLE 2.—RANGE OF VARIATIONS OF DUPLICATE DETERMINATIONS ON THE SAME SUBJECT.

	I (La. II and III).		II (Hi. II and IV).	
	(1)	(2)	(1)	(2)
Appearance time of glycosuria, min. . . . .	4	3	4	6
Blood sugar at appearance of glycosuria, % . . . . .	170	181	172	188
Blood sugar at disappearance of glycosuria, % . . . . .	150	150	154	170
Volume of urine, cc. . . . .	111	74	102	78
Duration of glycosuria, min. . . . .	5	9	9	11

2 patients. With our technique it is apparently possible to reproduce the appearance of glycosuria within 10 to 15 mg.%. This appears to represent the experimental error of the method. Hence, threshold values agreeing within this range can be considered constant and they indicate that our method of procedure does give results reproducible within this range.

In the cases where doses larger or smaller than 10 gm. were injected the appearance levels tended to become respectively higher or lower so that the higher the concentration of the sugar is raised in the blood the higher the value at which glycosuria will appear.

**The Disappearance Level of Glycosuria.** Our disappearance levels were always lower than the appearance levels and covered a wider range. In 7 of 21 cases they were at or below 120 mg.%, *i. e.*,



in the normal aglycosuric range. As others have pointed out,<sup>1,9</sup> the disappearance level of glycosuria does not appear to be an accurate criterion of the ability of the kidney to hold sugar, although there seems to be a certain correlation between the heights of the appearance and the disappearance levels. The correlation index is 0.85 but, because of the small number of samples available, is of doubtful significance. Our impression is that with increased doses of glucose the whole glycosuric range is pushed up on the blood sugar scale. This means that the greater the hyperglycemia produced in a tolerance test, the higher the level at which glycosuria will begin and end.

**The Duration of Glycosuria.** In 2 of our 19 experiments using 10 gm. of glucose there was no glycosuria; in 8 the duration was 15 minutes or less; in 4 it was between 15 and 26 minutes; in 3, between 26 and 37 minutes; and in 2 others the glycosuria had not ceased at the end of over 40 minutes when the experiments terminated. The fact that in these last experiments very small amounts of urine were voided indicated that the duration of glycosuria might depend in part upon the volume of urine produced or the speed with which it was put out.

As a result of this observation, 1000 cc. of fluid were given by mouth to 1 patient during the 2 hours preceding the test. Her urinary output upon the first occasion was 23 cc., but with the fluids it was raised to 310 cc. and the disappearance of glycosuria was reduced from more than 40 to 5 minutes. Another patient who received no fluids showed glycosuria for 25 minutes and a urine volume of 57 cc. In 2 subsequent experiments this period was reduced to 9 and 5 minutes with urine volumes of 74 and 111 cc. respectively by the administration of 1000 cc. of fluid. One patient who seemed to fall entirely out of line voided only 15 cc. of urine, the smallest amount in the series, and showed glycosuria for only 4 minutes. She had received only 8.8 gm. of glucose. She had been allowed fluids *ad lib.*, but as the actual amount taken was not measured, no point can be made of the result. A statistical analysis of our cases showed an index of correlation between the volume of urine and the duration of glycosuria of  $0.6542 \pm 0.0863$ , a figure of uncertain significance with such a small number of cases. There was no demonstrable relationship between the duration of glycosuria and the appearance time, perhaps because the latter was usually so short that the error in determining it obscured any variation that might have occurred.

One factor, not capable of perfect control, was the completeness with which the bladder, kidney, pelvis, etc., was emptied at each sample. This, if not done, could extend the disappearance time and hence the duration. Some of the irregularities may be explained on this basis, although the greatest care possible was used in attempting to clear the bladder of urine at each collection.

**Discussion.** Our results from the intravenous injection of doses of glucose varying from 7.5 to 20 gm. may be summarized as follows: Usually 3 to 8 minutes were required for the appearance of glycosuria but not infrequently this period was lengthened, and in 1 case no sugar appeared in the urine until 32 minutes after injection. During this time the blood sugar values had passed the maximum and were diminishing. With the same dose, the appearance level was constant for an individual but varied with different people. With the same person it varied with the dose. The disappearance level was lower than the appearance level and while less constant, it did depend to some extent upon the latter value. The smaller the volume of urine voided, or the slower the rate, the longer did glycosuria persist.

In the absence of definite knowledge of the mechanism involved, speculation is more or less futile, but it may be presumed that the tubular absorption of glucose may for a while be able to remove the increased quantity in the glomerular filtrate. After a period of variable duration the absorptive power weakens and glycosuria ensues.

Höber has recently<sup>2</sup> recalled a suggestion originally made in 1899,<sup>3</sup> that glucose is absorbed by the formation of some intermediary compound in the tissues. Experimental evidence has recently been advanced,<sup>4,5,12</sup> indicating that this is one of the hexosephosphates and that absorption both from the alimentary tract and through the kidney tubules is dependent on this process. It has been shown that phlorizin acts by interfering with the formation or decomposition of this compound with a resultant excretion of sugar.<sup>2,10</sup> It would seem that the glycosuria produced in our experiments may have been due to a failure in the same process though a failure of a different nature.

In the glycosuria of phlorizin poisoning the tubular resorptive mechanism is so severely damaged that it either fails completely or if it functions at all it does so only at a greatly reduced efficiency. With hyperglycemic glycosuria there are two possibilities: (1) The mechanism may be as active as usual but simply unable to transport more than a fraction of the increased burden of glucose presented to it, leaving an excess to escape through the ureter, or (2) the capacity of the machine may be reduced by the exhaustion of one of its elements, *e. g.*, the phosphate or one of the enzymes involved. The second case resembles that of phlorizin poisoning, though in the latter an enzyme is apparently inactivated and not merely depleted.

If one makes the simplifying assumption that sugar passes through the glomerulus so rapidly that this process does not become a limiting factor in the subsequent events, the appearance of sugar in the urine, if the first condition holds, should take place as soon as the blood sugar has reached a point where the sugar in the urine

exceeds the capacity of the tubular absorptive mechanism to remove it completely. Since the urine is promptly carried beyond the tubules, glycosuria should cease as soon as the blood sugar level has fallen to the point where all of the sugar can be removed. In other words, since intravenous injection of glucose causes an almost instantaneous rise in blood sugar, the appearance of glycosuria should be very prompt in all cases where the proper height of blood sugar is reached. The delays of 3 to 8 minutes which were commonly found seem to be too long. There should be no noticeable difference in appearance time since the time required to reach the blood sugar peaks were identical within our ability to measure them.

The disappearance levels should coincide with the appearance levels. And since the blood sugar was changing much more slowly when glycosuria disappeared, and hence these figures could be caught more accurately, they should be more constant than the appearance values. The opposite was found.

On the other hand, if some element in the system had to be used up this might require not only a measurably long period but also one which would vary with the supply of the material present, the rapidity with which it could be restored and the rapidity with which it was being exhausted, *e. g.*, from a continued high blood sugar. Also since in any case time would be required for its replacement, a lag in the disappearance level of blood sugar would result. In other words the appearance of glycosuria should lag behind the injection and the disappearance level should be lower than the appearance level. It should be more variable but with some degree of dependence upon it.

Finally, under the first condition the slower the flow of urine, the more completely could the sugar be removed and the more rapidly would glycosuria disappear. A slow secretion could compensate for a high sugar concentration. On the other hand, if the renewal of the sugar-absorbing mechanism depended on the replacement of some constituent supplied by the urine, *e. g.*, inorganic phosphate, the longer would glycosuria continue if the supply of urine were reduced. This is what does happen.

If one accepts the suggested part of phosphorylation in glucose absorption, a new significance is given to the results of Wilder and Sansum,<sup>11</sup> who found that glucose could be injected at the rate of 0.85 gm. per kilo per hour without glycosuria. This may represent a maximum rate at which the phosphorylation mechanism can operate. In our cases of hyperglycemic glycosuria this maximum rate was exceeded, some element in the phosphorylation mechanism, such as the store of phosphate or of enzyme in the tubular membranes, became exhausted, adequate resorption of glucose was prevented, and sugar appeared in the bladder urine.

**Conclusion.** A study of the relationships between hyperglycemia and glycosuria after the intravenous injection of glucose indicates

that the excretion of sugar may be explained on the basis of the suggested participation of phosphorylation in the resorption of glucose from the glomerular filtrate.

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## VARIATIONS IN BLOOD PRESSURE IN RENAL TUBERCULOSIS.

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THE opinion is generally expressed<sup>6,7</sup> that patients who have an active tuberculous lesion usually exhibit an arterial tension lower than normal regardless of the situation of that lesion. For that reason we were interested to determine what the ranges of blood pressure would be among subjects who had renal tuberculosis, inasmuch as a study of an adequate series from this standpoint had not been reported in the literature. Ayman stated that arteriolar essential hypertension and active tuberculosis do not commonly occur together, but he offered no explanation for this. A recent analysis of the blood pressures of tuberculous patients encountered in dispensary practice was made by Bunta, who commented on his findings by saying that progressive lowering of the blood pressure paralleled tuberculous activity. He felt that hypotension was not an absolute rule in tuberculosis, but that the trend of individual measurements of blood pressure toward normal spoke

well for the ultimate arrest of the disease, and that a progressive lowering of the blood pressure called for a guarded prognosis.

It has been postulated<sup>3</sup> that action of the tuberculous toxin on the vasodilator center is the factor which results in an arterial tension lower than normal in tuberculous patients. Fishberg<sup>5</sup> stated that "blood pressure is lower than normal in the vast majority of phthisical patients, evidently due to the toxic effects of the metabolic processes of the tubercle bacillus, because an injection of tuberculin is usually followed by a fall in blood pressure."

TABLE 1.—SYSTOLIC BLOOD PRESSURES OF 229 MALES WITH RENAL TUBERCULOSIS.

Systolic blood pressure, mm. mercury.	Age, yrs.												Total.	Per cent.
	10 to 14.	15 to 19.	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.		
90 to 99	..	..	..	..	..	1	..	..	..	..	..	..	1	0.4
100 to 109	..	..	..	3	6	2	4	6	4	..	..	1	26	11.4
110 to 119	..	3	4	11	13	8	5	5	2	3	1	..	55	24.0
120 to 129	3	5	7	6	9	11	8	4	5	1	..	..	59	25.7
130 to 139	..	2	1	4	8	7	6	7	1	2	..	..	38	16.6
140 to 149	..	..	3	..	5	7	3	1	5	3	..	..	27	11.8
150 to 159	..	..	2	..	1	..	..	1	2	..	2	..	8	3.5
160 to 169	..	..	1	..	..	1	1	1	2	1	..	..	7	3.0
170 to 179	..	..	..	1	..	1	..	1	..	..	1	..	4	1.7
180 to 189	..	..	..	..	..	1	..	1	..	1	..	..	3	1.3
190 to 199	..	..	..	..	..	..	..	..	..	..	..	..	..	..
200 to 209	..	..	..	..	..	..	..	..	..	..	..	..	..	..
210 to 219	..	..	..	..	..	..	..	1	..	..	..	..	1	0.4
Average . .	124	123	130	120	121	128	124	130	129	136	147	102	126.9	
Total patients .	3	10	18	25	42	39	27	28	21	11	4	1	229	

We analyzed the systolic blood pressures in 346 unselected cases of renal tuberculosis in which patients were admitted to The Mayo Clinic between 1925 and 1934, inclusive (Tables 1 and 2). Nephrectomy was carried out in each case and in each case the clinical diagnosis of renal tuberculosis was substantiated. Of the 346 patients, 117 were females and 229 were males, their ages ranging from 11 to 68 years. The left kidney was involved in 167 cases, the right in 169 cases and in 10 cases both kidneys were involved. Acid-fast bacilli were isolated from the urine in 258 cases (74.5%). The renal lesion was active in every case, which was demonstrated at the time of nephrectomy, and there was almost complete destruction of the involved kidney in most cases. Adequate renal function was the rule, as was evidenced by the fact that of 245 cases in

which the blood urea was estimated, in only 27 was the value more than 40 mg. per 100 cc.

TABLE 2.—SYSTOLIC BLOOD PRESSURES OF 117 FEMALES WITH RENAL TUBERCULOSIS.

Systolic blood pressure, mm. mercury.	Age, yrs.												Total.	Per cent.
	10 to 14.	15 to 19.	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.		
80 to 89	..	1	..	..	..	..	..	..	..	..	..	..	1	0.9
90 to 99	..	..	..	1	1	1	1	..	..	..	..	..	4	3.4
100 to 109	..	2	1	2	5	1	4	..	..	..	..	..	15	12.8
110 to 119	..	..	6	1	9	5	2	2	2	..	..	1	28	23.9
120 to 129	..	..	1	5	7	9	1	4	2	1	1	..	31	26.5
130 to 139	..	..	1	1	2	1	3	1	2	2	..	..	13	11.1
140 to 149	..	..	..	1	3	1	2	1	2	..	..	1	11	9.4
150 to 159	..	..	..	1	1	..	..	1	1	..	..	..	4	3.4
160 to 169	..	..	..	..	..	..	1	2	2	1	..	1	7	6.0
170 to 179	..	..	..	..	..	..	1	..	..	..	..	..	1	0.9
180 to 189	..	..	..	..	..	..	..	2	..	..	..	..	2	1.7
190 to 199														
200 to 209														
210 to 219														
Average . .	..	99	115	121	119	120	125	141	138	139	120	137	124.5	
Total patients .	..	3	9	12	28	18	15	13	11	4	1	3	117	

A systolic blood pressure of between 100 and 140 mm. of mercury was regarded as normal. Of the males, 77.7% and of the females, 74.4% had systolic blood pressures in this normal range. The systolic blood pressures of 21.8% of the males and of 21.4% of the female was 140 mm. of mercury or more; 0.4% of the males and 4.3% of the females had a systolic pressure less than 100. In Figs. 1 and 2 the actual readings of systolic blood pressure for each of the 229 males and 117 females, respectively, are recorded. The mean value for each age group was superimposed in the form of a curve, and for purposes of ready comparison we have added a control curve, obtained by an analysis of the systolic blood pressures of 1668 normal males and 1202 normal females.\* It is obvious that the average systolic blood pressures of males and females who have renal tuberculosis closely parallels the average readings for normal individuals, and when plotted as a graph form a gently upswinging curve, for the most part lying between the limits of 120 and 130 mm. of mercury and reaching its peak in the upper age groups.

In a consideration of the whole group, 265 patients (76.58%) had a systolic blood pressure reading between 100 and 139 mm. of

\* Unpublished work by Alvarez and Berkson of The Mayo Clinic.

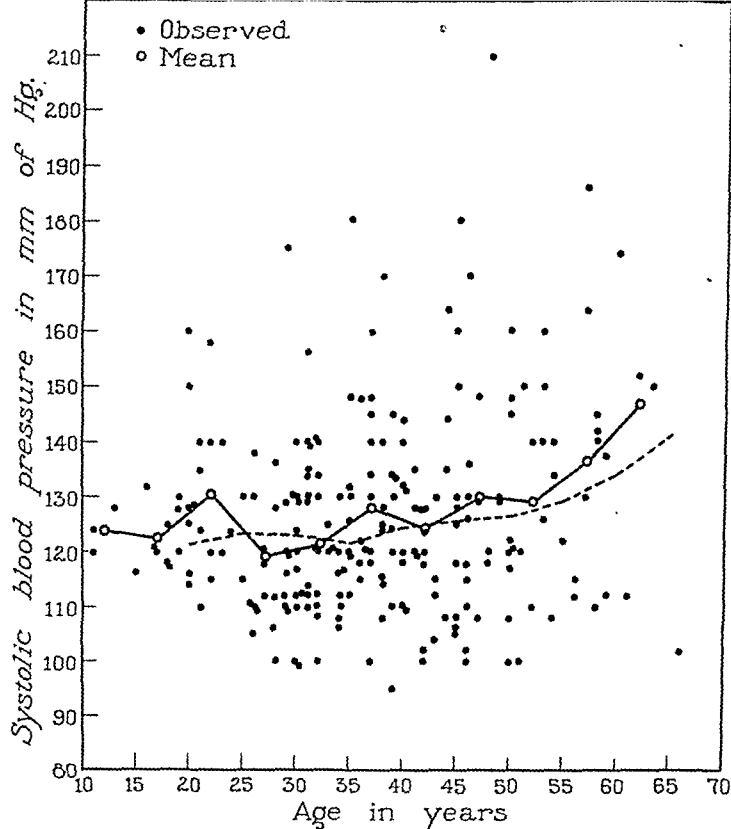


FIG. 1.—Systolic blood pressures of 229 males with renal tuberculosis. The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of 1668 normal males.

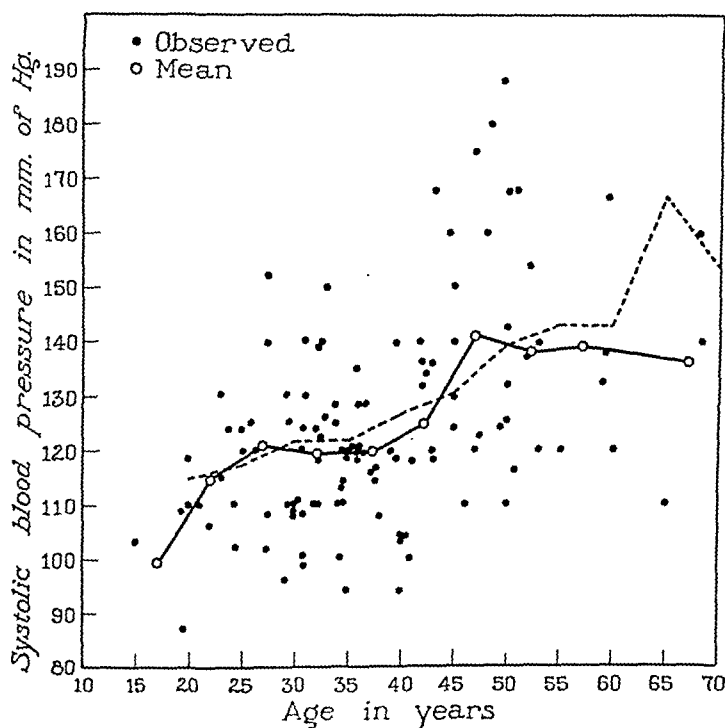


FIG. 2.—Systolic blood pressures of 117 females with renal tuberculosis. The continuous line is the curve of the mean systolic blood pressures. The broken line is a curve representing the mean systolic blood pressures of 1202 normal females.

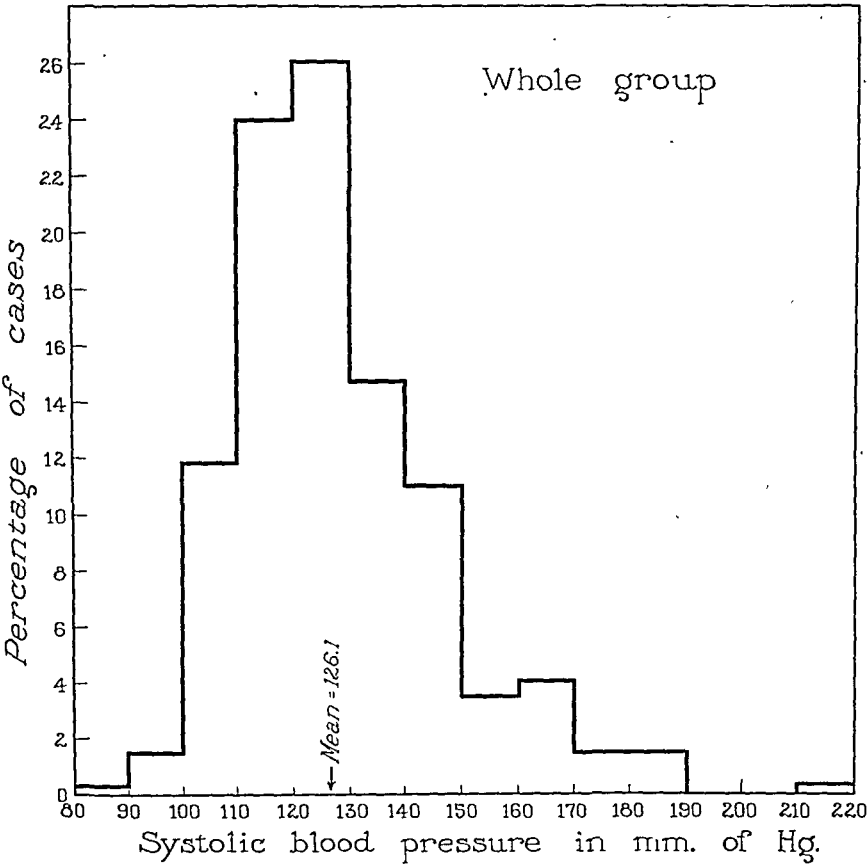


FIG. 3.—Percentage incidence of various levels of systolic blood pressure (in units of 10 mm. of mercury) in the whole group of 346 patients who had renal tuberculosis.

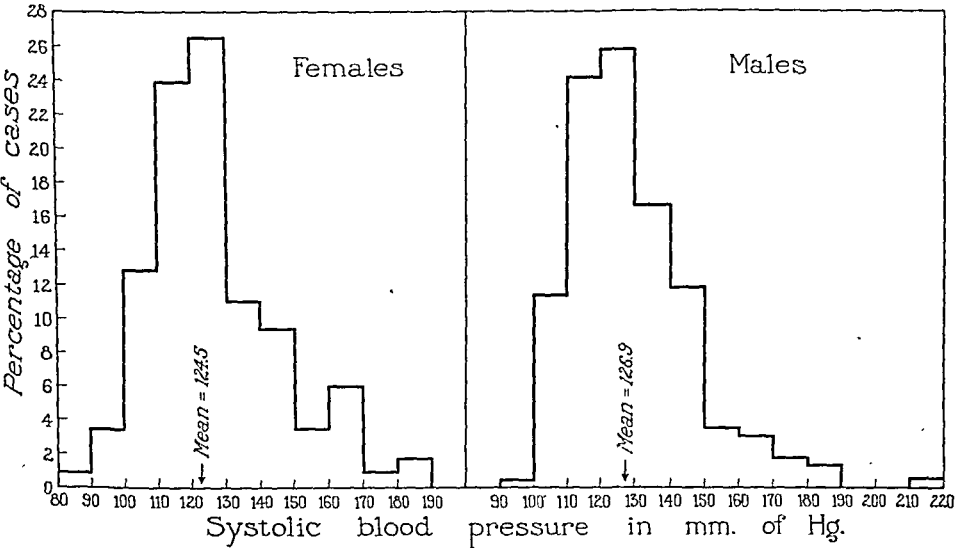


FIG. 4.—Percentage incidence of various levels of systolic blood pressure (in units of 10 mm. of mercury) in 229 males and 117 females who had renal tuberculosis.



mercury, inclusive; 6 (1.72%) had a reading less than 100; and 75 (21.64%) had a reading of 140 or higher. The lowest reading recorded was 86, the highest 210. The mean value for the whole group, obtained by averaging the recorded values, was 126.1 (Fig. 3). When a further consideration was made of males and females separately, there was found to be no essential sex variation (Fig. 4); 77.7% of the males and 74.4% of the females had a systolic blood pressure ranging between 100 and 139 mm. of mercury. The mean systolic value for the males was 126.9 and for the females 124.5.

**Summary.** As a result of the analysis of the systolic blood pressures of 346 patients who had proved renal tuberculosis, we cannot concur in the opinion generally expressed, that an active tuberculous lesion, regardless of its situation, has an accompanying arterial tension lower than normal. In the series of cases analyzed it was found that the vast majority of patients (approximately 76%) had normal blood pressures, 22% had hypertension, that is, a systolic pressure of 140 mm. of mercury or more, and approximately 2% had hypotension, that is, a systolic blood pressure less than 100 mm. of mercury. The number of patients in this series with hypertension or hypotension was not any greater than was found in a larger control series of normal individuals in the same age groups.

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## FACTORS CONDITIONING THE TRANSMISSION OF SYPHILIS BY BLOOD TRANSFUSION.\*

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It is a well established fact that the virus of syphilis may be transmitted by blood transfusion. A recent incident in my own

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experience has emphasized the necessity of clarifying our knowledge concerning this therapeutic accident. A colleague is involved in litigation as the result of having given a transfusion with blood from a donor who later was found to have syphilis. The recipient subsequently was also found to have syphilis and a malpractice suit was instituted on the grounds that the disease had been acquired through the medium of the blood transfusion. In this instance the importance of being able to say what is and what is not "transfusion syphilis" is obvious. While a good deal has been written on the subject, most of the papers in the literature consist of case reports. In the present study an effort was made to analyze the data and to relate the information thus obtained to our knowledge of the human and experimental disease. It was done with the hope that the knowledge thus acquired would make it possible to define clearly the clinical features of "transfusion syphilis" and to state the circumstances under which it may develop.

*Material.* In 1915 Fordyce first recorded the transmission of syphilis by blood transfusion. Bernheim in 1917 gave an undetailed account of its occurrence once in his experience.<sup>1</sup> In recent years cases have been reported with increasing frequency. These have been reviewed and tabulated and an additional case from the Vanderbilt University Hospital added (Table 1.) Several reports in the literature were not considered to have been founded on conclusive evidence, or were too incomplete to allow for analysis, and were therefore not included.

In all there were found to be 16 indubitable cases of syphilis acquired through blood transfusion. In every instance the disease made itself apparent by the development in the transfusion recipient of generalized lesions (skin, mucous membranes). In all instances in which the incubation period could be determined, it was found to be between 4 and 14 weeks. Every case of "transfusion syphilis" apparently developed the picture of the generalized, secondary stage of the disease and this within from 1 to 3½ months after the transfusion. The literature contains no instance of latent or active chronic syphilis which was acquired through blood transfusion without having passed through a readily recognizable acute stage. It would seem that the introduction of the virus directly into the blood stream invariably results in acute manifestations of the generalized infection.

An analysis of the table as regards the donors is enlightening. The status of syphilitic infection in the donors could be determined in 11 of the 16 reports analyzed. Of these 11 donors 9 had either primary or secondary syphilis at the time of the transfusion. Another donor gave blood 4 days before the appearance of the chancre. Thus 10 of the 11 donors had acute syphilis. In 1 instance (Spillman and Morell) the blood donor was presumably infected by the recipient's blood through an interchange of cannulae. The

recipient, a woman, subsequently died of postpartum hemorrhage. She had had 3 miscarriages and her husband was known to have syphilis. With the single exception, then, of syphilis related to pregnancy all of the donors whose syphilitic status could be determined had early, acute syphilis. Not a single instance of indubitable "transfusion syphilis" has been reported in which the disease was induced by blood from a donor with well established latent or chronic syphilis uninfluenced by pregnancy.

TABLE 1.—DATA IN 16 CASES OF TRANSFUSION SYPHILIS.

Author.	Type of syphilis present in donor ("acute" indicates primary or secondary stage).	Incubation period in recipient.	Clinical manifestations of syphilis in recipient.	Reference.
1. Fordyce, J. A. 2. Brem, W. V.	Acute syphilis Acute syphilis	Not stated Not given	Generalized eruption Generalized eruption, presumably. Described as "virulent" syphilis	Am. J. Med. Sci., 149, 781, 1915 J. Am. Med. Assn. (Discussion) 81, 535, 1923
3. Spillman, J., and Morell,	Generalized eruption developed 1 month after transfusion	One month	Chronic syphilis; pregnancy	Bull. Soc. franç. de dermat. et de syph., 33, 453, 1926
4. Levy, I. I., and Ginsberg, L. 5. Feldman, V.	Acute syphilis Acute syphilis (recurrent secondary)	2 to 3 months Within 3 mos.	Generalized eruption Generalized eruption	Am. J. Syph., 11, 447, 1927 Arch. Dermat. and Syph., 18, 380, 1928
6. Constantinescou, E., and Vatanu, N. 7. Aubertin, C., and Fleury, J.	Acute syphilis Undetermined	2½ months 9 weeks	Generalized eruption Generalized eruption	Ann. d. mal. ven., 24, 161, 1929 Bull. et. mem. Soc. méd. d. hôp. de Paris, 54, 69, 1930
8. Gougerot, Fiesinger, Bruno and Dally 9. Polayes, S. H., and Lederer, M.	Acute syphilis Undetermined	3 months 3½ mos. (approximate)	Generalized eruption Generalized eruption	Ann. d. mal. ven., 26, 174, 1931 Am. J. Syph., 15, 72, 1931
10. Pinard, M., and Robert, P. 11. Post, C. D., and Cooney, G. C.	Not determined; probably acute (laryngitis) Acute syphilis, incubation stage; developed chancre 4 days after giving transfusion	10 weeks 3 months	Generalized eruption Generalized eruption with meningeal signs	Bull. et. mem. Soc. méd. d. hôp. de Paris, 48, 214, 1932 J. Am. Med. Assn., 100, 258, 1933
12. Williamson, G. R. and Strong, R. A. 13. Moore, J. E.	Not determined Acute syphilis (chancre)	6 weeks 4 to 6 weeks	Generalized eruption Secondary syphilis	Am. J. Syph., 17, 484, 1933 The Modern Treatment of Syphilis, Chas. C Thomas Baltimore, p. 456, 1933
14. Moore, J. E. 15. Moore, J. E. 16. Author's case	Acute syphilis (chancre) Not stated Acute syphilis	4 to 6 weeks 5 weeks 5 to 8 weeks	Secondary syphilis Secondary syphilis Secondary syphilis	Cited by Moore, J. E.

\* In this case the transfusion donor received some of the recipient's blood, presumably through an exchange of cannule, and developed acute syphilis 1 month later.

**Discussion.** The relation of these clinical observations to other facts pertaining to both the experimental and human disease is enlightening. Since the virus of syphilis must be present in the blood of the donor if transfusion is to result in the establishment

of syphilitic infection in the recipient it would seem fitting to review first what is known concerning this point.

In the experimental disease in rabbits it has been shown that the virus of syphilis is present in the blood during the acute or active phase of the infection. With the disappearance of active lesions the blood loses its capacity to infect.<sup>2</sup> During latency, or inactive infection, the reservoir for *Treponema pallidum* is chiefly lymphoid tissue and not blood. This has been repeatedly demonstrated. That this is also true in the human disease was shown by Eberson and Engman<sup>3</sup> in 1921. Blood from 73 individuals with latent or chronic visceral syphilis was shown to be non-infectious when injected into rabbits' testicles. In a review of the literature these authors stated that the blood in chronic human syphilis had never been shown to be infectious for rabbits save in 1 case reported by Uhlenhuth and Mulzer.<sup>4</sup> This patient was a woman who had been delivered of a syphilitic fetus 18 days before the specimen of blood was obtained for examination. Moore<sup>5</sup> summarizes the matter as follows: "With the spontaneous healing of lesions it is probable that treponemes disappear from the blood to gain entry again, if at all, only in small and irregular showers during the period in which relapsing infectious lesions are prone to occur. After latency is firmly established the virus cannot be demonstrated by animal inoculation and it is probable that except in one special circumstance organisms are actually absent. The special circumstance is pregnancy. . . . their presence in the mother's blood at some stage of pregnancy must be assumed."\*

There is considerable evidence that not only will blood from individuals with chronic syphilis fail to induce the disease in rabbits but that it will also fail to transmit the disease to humans. Tzanck and Werth<sup>6</sup> record the case of a donor with seronegative latent syphilis who gave 18 transfusions without having once transmitted the disease to the recipients. This donor subsequently developed active neurosyphilis. It has been said that in Germany blood from cases of general paresis with *malaria inoculate* is frequently used in order to induce malaria in non-syphilitic patients.<sup>7</sup> There are no recorded instances of syphilis thus induced. McNamara<sup>8</sup> deliberately transfused 10 non-syphilitic patients with blood from 6 cases of chronic syphilis. In not a single instance was syphilis induced in the recipients, although 4 of the 10 received transfusions from 2 syphilitic donors and 1 recipient was transfused from 3 syphilitic donors.

While it is admittedly possible that syphilis may be induced by blood transfusion without the appearance of skin or mucous membrane lesions in the recipient—that is, without any clinical manifestations of the acute state of the disease—our methods at the present

\* This assumption unquestionably holds in the cases reported by Uhlenhuth and Mulzer, and Spillman and Morell, loc. cit.

time render impossible the discovery of such cases. It is possible that the direct introduction of the virus in the blood stream, thus depriving the recipient of any possible beneficial (immunizing) effects of skin or mucous membrane inoculation, lymphatic infection and chancre formation, insures the development of an invariably active type of acute skin and mucous membrane syphilis. The observation of Brown and Pearce<sup>9</sup> that excision of the chancre in acute syphilis in the rabbit may result in a greater incidence of generalized lesions may have some bearing on this point, in spite of the fact that it was subsequently shown by Chesney<sup>10</sup> that this does not always hold true. In this connection it is also noteworthy that the intravenous injection of virus in experimental syphilis leads to the development of malignant bone lesions. These lesions are far greater in extent and severity than the bone lesions developing in the course of an experimental infection in rabbits engendered by intratesticular or intradermal inoculation.<sup>11</sup>

**Summary.** From the literature 15 cases of syphilis induced by blood transfusion have been collected and to these an additional case has been added.

An analysis of this material reveals that in every instance the disease made itself apparent in the recipient by the development of the generalized skin or mucous membrane lesions of acute syphilis. We have encountered in the literature no instance in which syphilis was acquired by blood transfusion without the development of these acute, secondary lesions.

The incubation period between the time of transfusion and the first appearance of secondary lesions has varied in the reported cases from 4 to 14 weeks.

The stage of syphilitic infection present in the donors could be determined in 11 of the 17 case reports. One donor was in the incubation stage of acute syphilis and gave blood 4 days before the appearance of the chancre; 9 had either primary or secondary syphilis at the time blood was drawn for transfusion. In the remaining instance the donor was infected by an interchange of cannulæ while giving blood in a case of postpartum hemorrhage in a syphilitic woman. Not a single instance of incontestable "transfusion syphilis" has been reported in which the disease was transmitted by blood from a donor with latent or chronic syphilis uninfluenced by pregnancy. In repeated instances donors with chronic syphilis have failed to transmit the disease.

The above observations have been shown to be consistent with our knowledge of the pathogenesis of the experimental and human disease.

**Conclusion.** 1. The transmission of syphilis by blood transfusion in the reported cases in the literature has been manifested in the recipient by the development of the acute secondary stage of the disease within from 1 to 3½ months after the transfusion. Our

present knowledge does not allow of a diagnosis of "transfusion syphilis" in the absence of such developments in the recipient.

2. Syphilis is obviously transmissible by blood transfusion when, and only when, the virus is present in the donor's blood. Spirochetemia is known to occur only during the early stages of the infection before the development of latency, or during pregnancy in the chronic disease. Our present knowledge does not allow of a diagnosis of "transfusion syphilis" in the absence of these stages of syphilitic infection in the donor.

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### THE EARLY RESPONSE TO VENESECTION WITH OBSERVATIONS ON SO-CALLED BLOODLESS VENESECTION.

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VENOUS pressure is recognized as often elevated in cardiac failure, particularly in the congestive type (Frey,<sup>8</sup> Gaertner,<sup>10</sup> Hooker and Eyster,<sup>13</sup> Clark,<sup>3</sup> Eyster and Middleton,<sup>5</sup> Villaret, Saint Girons and Besançon,<sup>15</sup> Pogany,<sup>14</sup> and others). This has led a number of observers to suggest that venous hypertension be considered an early sign of impending or of existing cardiac failure, and that in such instances venesection might be of great value by reducing the excessive venous load with which the failing heart must contend (Eyster<sup>4</sup>).

The fact has apparently been overlooked that venous pressure and "venous load" are not necessarily the same, nor are they parallel

in all instances. Cases of severe cardiac failure are on record in which venous pressure was not elevated (Villaret, Saint Girons and Besançon,<sup>15</sup> Pogany,<sup>14</sup> Arnoldi,<sup>1</sup> Fuchs,<sup>9</sup> Harris<sup>11</sup>), and lesions of the tricuspid valve without heart failure are said to be associated with venous hypertension (Pogany<sup>14</sup>). Failures encountered after venesection may be due (1) to the fact that eventually the myocardium is no longer capable of favorable response, or (2) the possibility that the venous hypertension is essential for effective cardiac function. Even in the experimental animal it has been shown that improvement does not always follow venesection when the heart is overdistended (Brams and Katz<sup>2</sup>).

Our experiments were planned to study the early effects of clinical venesection on pulse rate, venous pressure, and on systolic and diastolic arterial pressures in patients with varying degrees of cardiac failure. An attempt was made also to study the same features after so-called "bloodless venesection" in the same patients, in order to compare the value of this procedure with ordinary blood-letting. It was also our purpose to determine the speed of inherent readjustment to venesection, in order to observe how soon and to what degree the effects of this procedure become nullified. These experiments for the study of venous pressure necessitated the employment of an accurate method which could be used for continuous observation over a prolonged period of time. This was accomplished by the use of the principle advocated by Moritz and v. Tabora, employing sodium citrate solution with frequent flushings of the tubing and needle. The apparatus was kept in faultless working condition for over 2 hours, without discomfort to the patient and without loss of accuracy in the readings.

A series of 15 patients was studied. Congestive cardiac failure was severe in 12 of these and moderate in the remaining 3. The clinical diagnoses were hypertensive heart disease, recent coronary occlusion, syphilitic aortitis, coronary sclerosis, and cor pulmonale. All patients were definitely dyspneic and showed varying engorgement of the cervical veins. Eleven showed definite venous hypertension during the control period, the lowest reading in this group being 14 cm. of water. Three had normal venous pressure and 1 showed a venous pressure of 1.9 cm. of water. We regarded the last as an instance of venous hypotension, having adopted a level between 5 and 10 cm. of water as the normal. Systolic and diastolic blood pressures by the usual auscultatory method, and the venous pressures and heart rates were determined under the basal conditions described by Eyster,<sup>4</sup> *viz.*, absolute bed rest for not less than an hour. The arm was abducted from the body in order to avoid the possibility of compression of the veins and resulting interference with the venous flow from the extremity. The needle and tubing were kept patent by using sterile sodium citrate solution and by frequent flushings of the system. Patency of the needle was tested

before and after each venous pressure reading. Observations of arterial and venous pressures and pulse rates were made at 5-minute intervals during a control period of 30 minutes, and at similar intervals for 1 hour after venesection was completed. Similar observations were made in patients subjected to "bloodless venesection" before and after the tourniquets were applied. Venesection was performed by inserting a large hollow needle in the cubital vein of the arm, the quantity of blood thus removed varying from 300 to 800 cc. "Bloodless venesection" was performed by applying tourniquets on each thigh and on one arm close to the trunk, sufficient

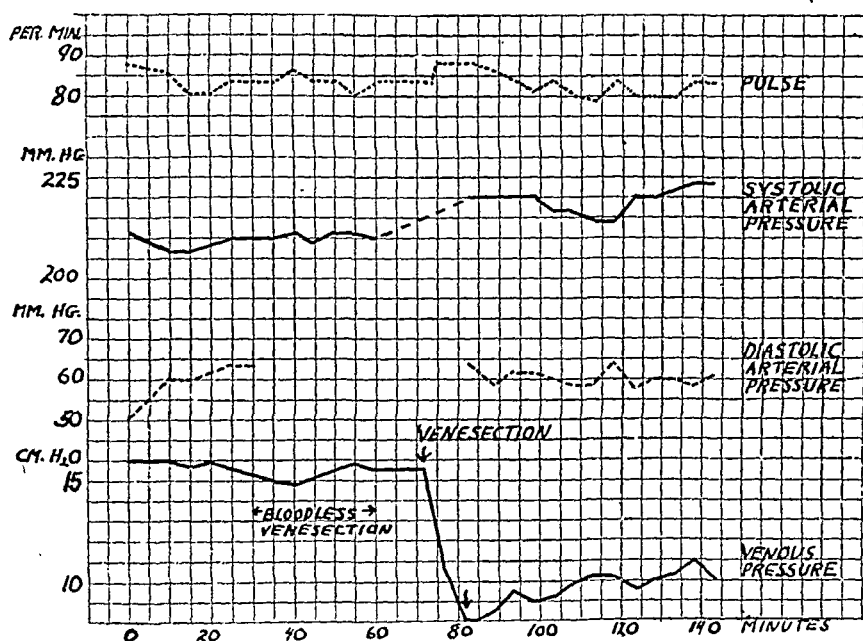


FIG. 1.—Illustrating effects of venesection on pulse rate, systolic and diastolic arterial pressure and venous pressure in Case 6, hypertensive myocardial disease with failure. "Bloodless venesection," shown by arrows, produced practically no change. Removal of 600 cc. blood, between arrows, resulted in an immediate drop in venous pressure with a slight tendency to return toward the control level later. This was associated with a practically unaltered rate, and systolic and diastolic arterial pressure levels.

compression being used to obstruct the veins without interrupting the arterial supply to the parts, as shown by persistence of the palpable pulse beyond the site of obstruction.

Ordinary blood-letting caused no appreciable change in pulse rate in any instance of this series. Similar negative results were observed after so-called "bloodless venesection" was performed.

In only 4 instances did systolic blood pressure fall appreciably immediately after blood-letting was completed, the fall in these patients varying from 19 to 26 mm. of mercury. In 3 of these, systolic pressure returned approximately to the control level within



an hour after venesection. In 4 instances diastolic pressure also fell appreciably immediately after venesection, the drop varying from 15 to 22 mm. of mercury, but here too there was a return in 2 instances to the previous level within an hour. Control systolic pressure was above 160 mm. of mercury in 7 instances, 5 of which showed readings above 200 mm. In these 7 cases of arterial hypertension there was only 1 in which venesection was followed by an appreciable immediate fall in systolic pressure, namely from 238 mm. to 212 mm. There was practically no change in the remainder of these patients. "Bloodless venesection" failed to induce any significant change in systolic pressure. Control diastolic pressure was above 100 mm. mercury in 6 instances, and in only 1 of these did venesection cause a fall of diastolic pressure. Only minor changes occurred in the remainder. In other words, the amount of blood removed, up to 800 cc., had no apparent consistent effect on either the systolic or diastolic arterial pressure except in the few instances previously noted. It was also apparent that no definite relation existed between the degree of change in blood pressure and the degree of change of venous pressure under the conditions of these experiments.

TABLE 1.—CHANGES IN VENOUS PRESSURE AFTER VENESECTION.

Experiment No.	Control venous pressure (cm. citrate sol.).	Quantity of blood removed (cc.).	Immediate drop (cm. citrate sol.).	Drop below control level 1 hour after venesection (cm. citrate sol.).
1	23.7	800	12.0 (50.6%)	6.9 (29.1%)
2	23.0	800	9.7 (42.2%)	9.3 (40.4%)
3	19.0	800	8.7 (45.8%)	13.0 (68.4%)
4	18.3	800	7.3 (39.9%)	2.3 (12.6%)
5	7.3	650	2.0 (27.4%)	1.8 (24.7%)
6	15.5	600	7.5 (48.4%)	6.5 (41.9%)
7	4.7	600	2.2 (46.8%)	1.5 (31.9%)
8	18.5	600	9.0 (48.6%)	7.0 (37.8%)
9	6.0	500	2.5 (41.7%)	1.5 (25.0%)
10	16.3	400	6.2 (38.0%)	2.0 (12.3%)
11	1.9	400	1.4 (73.7%)	1.5 (78.9%)
12	22.0	300	3.0 (13.6%)	10.0 (45.4%)
13	14.0	300	9.0 (64.3%)	2.0 (14.3%)

It will be noted that although the drop in venous pressure was greatest where the greatest quantity of blood was removed, it so happened that the pressure level returned nearer to normal in all but one of those cases where 500 cc. or less had been removed.

The removal of blood was followed by more consistent changes in venous pressure. Table 1 represents the changes observed immediately after completion of venesection and at a period 1 hour later. It will be observed that a fall in venous pressure occurred in every instance and that the control level was not reached again during the following hour, although a partial return was noted in 8 instances. The greatest initial drop occurred in those patients who had venous hypertension before venesection, the quantity of blood removed

playing a comparatively lesser rôle. The maximum fall occurred immediately after completion of venesection in all but 2 instances, and in 8 instances the venous pressure began to rise within a few minutes. No relation could be determined between the degree of fall in venous pressure and the height of control arterial pressure. There was no real effect after "bloodless venesection," venous pressure showing little change for a period of 30 minutes following application of the tourniquets. At most a slight fall or rise occurred, the maximum change in either direction not exceeding 2 cm. of water.

COMMENT. The results of these experiments indicate that the theoretical value of so-called "bloodless venesection" has no basis in fact, these findings being in accord with the observations of Fuchs.<sup>9</sup> No important modifications in arterial or venous pressure or pulse rate were observed in our own experiments. In some instances it was noted that the discomfort induced by the tourniquets resulted in a moderate rise in venous pressure which was not followed by a fall. Ordinary venesection in the same patient always produced some fall in venous pressure, even when the smaller quantities of blood were removed. These observations suggest that so-called bloodless venesection, as performed in these experiments, is of little value in reducing venous pressure or in modifying the pulse rate or arterial pressure in cardiac failure. We could obstruct only 3 limbs because it was necessary to use one arm for estimation of venous pressure, but it is doubtful if the results would have been different had all four extremities been obstructed.

The absence of change in pulse rate, even when as much as 800 cc. of blood was removed, suggests the probability that adjustments to the loss of such quantities of blood are easily attained. We believe that the beneficial effects of venesection are due in only a small part to change in pulse rate.

The changes in blood pressure observed in these experiments were neither uniform nor striking. There were only a few instances in which blood pressure fell after venesection, even when as much as 800 cc. of blood was removed. The same was true where arterial or venous pressures were excessively high before venesection. The prompt return within an hour toward the control level of both systolic and diastolic pressures, in all but 2 instances, again demonstrates the futility of venesection as a reliable method of permanently reducing arterial blood pressure. This is probably due to the many adjustments available to keep the arterial pressure constant, which would operate to modify the effects of venesection. The fact that arterial pressure varied only slightly in patients who showed definite and consistent changes in venous pressure after venesection, reëmphasizes the independence of control of arterial and venous circulation.

Changes in venous pressure after venesection were more consistent and more marked. A fall occurred promptly in every instance

regardless of the quantity removed, but this fall was generally more marked after removal of larger quantities of blood. The drop was most marked where venous hypertension existed before venesection, but even here, as in the majority of the experiments, a partial return toward the previous level occurred within a few minutes. This observation agrees with that of Eyster and Middleton,<sup>5,7</sup> who also found that the drop in venous pressure was more sustained and more marked in cases of venous hypertension. Our results also show the comparative sluggishness of compensatory adjustment in the venous system. The majority of the patients stated that they felt improved after venesection, but such results must be interpreted with caution, as it is probable that genuine improvement depends on more than mere reduction in venous pressure. For example, Hitzenger<sup>12</sup> found that venesection was followed by increased oxygen and decreased carbon dioxide content of the arterial blood, nor is it known how the blood reservoirs and other regulatory adjustments react after clinical venesection and we are not certain whether the "load" which the heart must pump is actually reduced after such adjustments take place. We do not wish to minimize the value of venesection in selected cases, but it is apparent that much study will be required to evaluate other factors such as circulating blood volume and minute volume output of the heart in order to determine the beneficial effects of blood letting.

RÉSUMÉ. 1. So-called "bloodless venesection" failed to reduce venous pressure or to modify pulse rate or arterial pressure in patients with cardiac failure. These results are in contrast to the changes observed in the same patients after blood letting.

2. The effects of ordinary venesection were studied in patients with cardiac failure. Observations were made every 5 minutes for a period of 1 hour after venesection was completed.

3. It was exceptional for either the systolic or diastolic arterial pressure to show an appreciable fall after venesection or during the period of observation. The same results were observed in patients with arterial hypertension as in those with normal pressure.

4. The pulse rate remained unchanged in all experiments.

5. Venous pressure fell consistently after blood letting, the maximum drop occurring immediately after completion of venesection. The fall began early in the course of venesection, becoming apparent after removal of the first 100 cc. of blood and continuing to drop as more blood was withdrawn. A partial return toward the control level within a few minutes was observed in the majority of instances, but the level of venous pressure after an hour was usually lower than the control level.

6. The fall in venous pressure was especially marked where venous hypertension existed and the actual drop also depended greatly on the quantity of blood removed. The greatest drop usually occurred where from 600 to 800 cc. of blood were removed in

cases of venous hypertension, though it so happened that a level that was nearer to normal was reached in the cases with a smaller blood removal.

7. The practical significance of the fall in venous pressure after venesection, in relation to cardiac failure, is briefly discussed.

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### PAIN IN THROMBO-ANGIITIS OBLITERANS: A CLINICAL STUDY OF 100 CONSECUTIVE CASES.

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PAIN is the most frequent symptom that leads a patient to consult a physician. Pain was the initial complaint in 90 of 100 consecutive cases of thrombo-angiitis obliterans. This study was undertaken in an endeavor to ascertain, classify, and describe the types of pain and the frequency of their occurrence in these cases of thrombo-angiitis obliterans, and to suggest, when possible, the mechanism by which such pain is produced.

In any study such as this it is well to emphasize that there are marked individual differences in the ability of the patient to feel pain, and that the threshold of sensitivity varies in the same person at different times. This has been emphasized by Libman.

A brief review of the innervation of bloodvessels seems pertinent to this discussion. The vessels of the extremities, according to Woollard, are supplied by vasomotor nerves in two ways, proximally from a continuation of the sympathetic plexuses about the aorta, and distally by branches from adjacent, mixed nerve trunks. In both instances the fibers are non-medullated, sympathetic postganglionic fibers. Peripherally, bloodvessels

receive a second type of innervation, namely, medullated or sensory fibers from proximal mixed nerves. These end in the adventitia and in surrounding tissue. The vessels in more distal parts of the extremities receive more branches from adjacent nerves than those situated proximally. On the basis of these facts it should follow that trauma to smaller vessels is more likely to cause pain than trauma to larger vessels. Two different pathways for the afferent conduction of such pain, one to nearby sensory roots, and the other up the sympathetic chain of ganglions, is the theory held by Foerster. The exact anatomic pathways are not known. Probably they are components of the thoracic spinal roots; to what extent they traverse the sympathetic trunks has not been determined. Odermatt found that sensory nerve endings are most abundant in the adventitia of the vessels, or on the surface of the media muscularis.

**Types of Pain in Occlusive Vascular Disease.** Pain in occlusive vascular disease may be the result of one or more of three factors: (1) that arising from the bloodvessels themselves, (2) that attributable to ischemia of tissue, including nerves, and (3) that attributable to infection.

*Pain Arising from the Bloodvessels.* This type of pain may be caused by spasm, stretching, or inflammation. Arterial pain is a characteristically constant, burning, gnawing pain, tending to spread out without reference to nerves. Barium chlorid, injected into arteries, causes a spasm of the smooth muscle, resulting in severe pain (Fröhlich and Meyer). We have observed prolonged spasm of the brachial artery, following perivascular neurectomy, which initiated a dull aching pain of the forearm and hand. There was no profound spasm of the smaller vessels, as shown by the color of the hand. Severe pain is rarely observed in the ischemic attacks in Raynaud's disease; the usual sensation is a dull, numb feeling. In operations under local anesthesia it has been noted that clamping or pulling an artery may give rise to pain. Bazett and McGlone demonstrated that simple arterial puncture caused a dull, aching, sickening pain which was diffuse in character, and was often referred to regions distal to the site of puncture. We have observed that puncture of smaller arteries is accompanied by more intense pain than puncture of larger arteries. Waterston reported similar observations. Odermatt was of the opinion that pain from injection of an irritating solution into an artery was produced in the finer arterial branches where the solution could penetrate the wall of the vessel and come in contact with sensory nerve endings. The endothelium of the vessel seemed to be insensitive to pain. He also demonstrated that pain may be elicited by distention of arteries, regardless of their caliber. The injection of solutions of sodium iodid into the femoral artery causes so much pain that general anesthesia may be required. Moore and Moore concluded that this pain was not the result of stretching of the vessel or contraction of its wall, but was produced in the finer arterial branches.

*Pain Attributable to Ischemia of Tissues.* Such pain is probably the result of ischemia of nerves. Ischemic neuritis is a misnomer,

as the lesion is one of degeneration from lack of adequate blood supply rather than of inflammation. Infiltration of nerve sheaths by an inflammatory process is a mild and late affair. In contracting muscle in which there is an inadequate supply of arterial blood, incompletely metabolized substances are believed to act as irritants to nerves, producing the characteristic symptom of claudication.

*Infection as a Cause of Pain.* Pain resulting from infection does not need elaboration here. It is important to realize that infection in tissue incompletely supplied with oxygen takes on different characteristics than in tissues with a normal supply of blood; local heat is absent and intensity of pain is heightened.

In view of these observations it is not surprising that pain should be an outstanding and early symptom of thrombo-angiitis obliterans, since the pathologic processes involve occlusion of major and minor arteries and veins, inflammation of vessels, skin, and muscle, ischemia of nerves, muscle, and skin, secondary, infectious, trophic changes in the skin, and vasospastic disturbances.

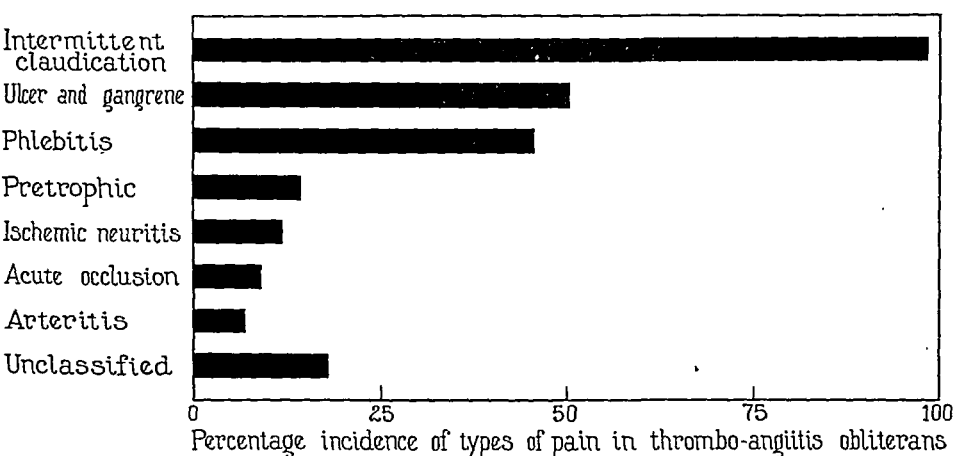


FIG. 1

*Pain Induced by Exercise and "Rest" Pain.* In this series of 100 consecutive cases of thrombo-angiitis obliterans two major groupings of pain were noted: (1) pain brought on by exercise, such as that of intermittent claudication and phlebitis, and (2) pain occurring during rest. Rest pain was further classified as pretrophic and trophic, the latter resulting from ulcers or gangrene; inflammatory, such as from arteritis or phlebitis; that due to acute occlusion with massive ischemia; that of ischemic neuritis; vasospastic, and unclassified. The incidence of these various types of pain is given in Fig. 1.

**Intermittent Claudication.** *Pain Related to Exercise.* Intermittent-claudication occurred in 98 of the 100 cases, marking the onset of symptoms of the disease in 75 (Table 1). The most frequent

sites of pain were the arch of the foot and the calf of the leg; it may occur, however, in any of the muscles of the extremity, in the toes, thigh, forearm, hand, or fingers. The pain which is induced by exercise is initiated with a feeling of dull aching fatigue, or sense of constriction in the affected muscles. If exercise is continued, a severe cramping pain develops which necessitates cessation of activity. Sensations of coldness and numbness may accompany the pain, or, in some cases, a sensation of burning. One patient described claudication as a feeling of tightness which persisted and increased in severity for a few seconds after he stopped walking, and then seemed to "flow away." The amount of exercise sufficient to produce claudication varies from walking a few yards to a mile or more, but in a given case it is remarkably constant. Repetition of a standard exercise test (120 steps per minute) in a group of patients revealed a variation in time of less than 10%. Nervousness, emotion, weather, and fatigue modify the time of onset of claudication in some subjects. In 4 cases the severity of claudication was increased by cold weather, in 1 by hot weather. The pain is relieved by a rest of from a few seconds to 10 minutes. After a period of rest the original exercise can usually be repeated. Fast walking will bring on claudication at a shorter distance than will slow walking. Walking uphill initiates the pain of claudication more rapidly than walking on level ground. As the occlusive process progresses proximally, claudication may progress from arch to calf to thigh, with a gradually diminishing walking distance. The progression of the disease may be vividly demonstrated by the decreasing tolerance to exercise.

TABLE 1.—INTERMITTENT CLAUDICATION IN 98 CASES OF THROMBO-ANGIITIS OBLITERANS.

Site of pain.	Right	Left.	Bilateral.	Time of onset.	Cases.	Status of claudication.	Cases.
Arch and foot	4	5	15	First symptom of disease	75	Progressive	38
Calf . . .	5	6	29	Less than 1 year after onset	10	Stationary	18
Arch and calf	8	8	16	1 to 3 years after onset	6	Improving	14
Thigh . . .	5	1	3	3 to 5 years after onset	3	Progressive, then improving	7
Palm and forearm	2	1	0	More than 5 years after onset	4	Unknown	21

The pain of claudication apparently is the result of some chemical substance formed during muscular contraction when the blood

supply is deficient. Roth has shown that the lactic acid of the veins of the affected extremity increases sharply after exercise in cases of occlusive disease of the arteries; an exact parallelism of the concentration of lactic acid with the intensity of the pain, however, is not demonstrated. The relationship of level of closure of arteries to the situation of the pain of claudication is important. It may be stated as a general rule that claudication in the muscles of the calf indicates occlusion of the popliteal arteries; if pain is limited to the feet, the dorsalis pedis and posterior tibial arteries are occluded. In 72 cases in which claudication in the muscles of the calf occurred, the popliteal vessels were graded 0 in 53, reduced in 10 (indicating pulsations palpable in collateral arteries), and graded 4 (normal) in 9. The probable explanation of claudication in these 9 cases is that the popliteal arteries were occluded at their bifurcation, although they pulsated normally in the region palpated. Conversely, a few patients with occluded popliteal arteries do not have claudication in the muscles of the calf. This could readily be explained on the basis of an exceptionally well-developed collateral circulation. In cases in which there is pain of claudication in the thigh, the femoral or iliac arteries are occluded.

The other type of pain that is induced by exercise occurs in certain cases of phlebitis, and it will be discussed in connection with that subject.

TABLE 2.—REST PAIN IN THROMBO-ANGIITIS OBLITERANS.

Time of onset of pain.	Pre-trophic.	Ulcer.	Gangrene.	Phlebitis.	Arteritis.	Acute occlusion.	Ischemic neuritis.
At onset of disease . . .	3	2	0	15	4	3	..
Within first year . . .	1	7	4	14	1	1	2
1 to 3 years later . . .	5	14	8	7	1	2	6
3 to 5 years later . . .	3	9	3	4	..	1	1
More than 5 years later . .	1	6	5	4	..	..	2
More than 10 years later .	1	5	3	2	2	2	1
<hr/>							
Severity of pain:							
Grade 1 (mild) . . .	1	4	1	10	2	4	2
Grade 2 . . .	3	5	3	2	..	..	2
Grade 3 . . .	2	21	9	3	1	5	4
Grade 4 (severe) . . .	..	2	4	0	..	..	3
Tenderness only . . .	..	..	..	15	1	..	..

**Pain Occurring with Rest.** *Pretrophic Pain.* Fourteen patients complained of rest pain which we have designated "pretrophic." This term is used because ulcers or gangrene frequently developed at the site of pain from a week to 6 months after its onset. Six cases are included under this heading in which trophic lesions failed to develop; we feel justified in thus classifying them, as the pain was of the same character, and often accompanied lesions on neighboring digits. This type of pain is well localized in the digits or in adjacent regions; it is described as a burning, gnawing type of pain, usually continuous and worse at night, or as an aching sensation



associated with local tenderness. In 2 cases it was intermittent in character. Four patients obtained relief on keeping the affected parts in a dependent position and 1 from walking; in 1 case exercise increased the discomfort. The time of onset of the pain in relation to the beginning of the disease and its severity are given in Table 2. The microscopic picture of the skin in these cases reveals a marked increase in fibrous tissue in the deeper layers (Figs. 2 and 3). This tissue contracts about the terminal nerve fibers causing irritation and ischemia, and is probably responsible for the pain. Another possible cause of pain is a small infarct, with inflammation of low grade eventuating in necrosis.

*Pain of Ulcers and Gangrene.* Ulcers or gangrene of one or more digits, with pain, developed in 50% of the cases studied. There were 17 patients who had both gangrene and ulcers, 26 with ulcers alone, and 7 with gangrene without ulceration. Ulcers were multiple in 25 cases, single in 18. A solitary area of gangrene was noted in 13 cases, multiple areas of gangrene in 11. The onset of pain with these trophic lesions was gradual, the severity increasing as the ulcers or gangrene progressed. The pain was described as burning, stinging, or tingling and was localized in the region of the lesion. It was usually continuous; in a few cases, however, it was paroxysmal. Some patients used the adjectives, "deep," "grinding," "driving," and "aching" to describe it. Projection of the pain was rarely observed. Marked hyperesthesia about the lesion was frequent. In 24 cases the pain was more severe at night, and in 18 relief on dependency was an important feature. These patients often slept sitting in a chair, or with the foot hanging over the side of the bed. External heat, by means of a baker, often aggravates the pain. Gangrene occasionally develops without any pain. This occurred in 1 case in this series.

Trophic pain was relatively rare in the first year of thromboangiitis obliterans (Table 2), and not infrequently occurred 5 and 10 years after the probable onset of the disease. It was often severe, the intensity being graded 3 or 4. The chronicity of pain resulting from ulcer is worthy of emphasis; it often lasts for months. The primary cause of this type of pain is probably secondary infection or localized edema. Slow healing is characteristic, owing to the ischemic state of the tissues. It is difficult to explain why dependency should give relief from pain. We have noted that the temperature of the skin is not consistently or significantly raised while the extremity is in this position. Elevated venous pressure, creating stasis of blood in the extremity, possibly is a factor.

Nocturnal exacerbation is characteristic of many types of distress. In explaining this one must consider that there are no external factors to divert the attention of the patient from his pain, and it thus occupies a central position in his mind. Possibly also the

lowering of metabolic processes and of systemic blood pressure play a part in increasing ischemia.

*Pain of Inflammatory Lesions of the Bloodvessels.* Localized inflammatory lesions, namely, phlebitis and arteritis, occurred in 46 and 7% of the cases, respectively. In 18 cases there was but one attack of phlebitis; in 11 cases two attacks, and in 16 phlebitis occurred on a number of occasions, at times being almost continuous. Phlebitis was superficial in 44 cases, deep in 2, and both superficial and deep in 2 others. It was the first symptom of the disease in 15 cases, and often occurred early in its course (Table 2). When phlebitis occurs in the feet, pain on standing or walking is induced. Pressure on and movement of inflamed tissues cause the pain, which does not simulate the distress of claudication resulting from a given amount of exercise.

**Case Report.** A man, aged 29, of Dutch ancestry, was first seen at the Clinic February 4, 1929. Six months previously, red tender nodules had developed along the course of the veins of the right calf. There was associated muscular soreness and stiffness. Phlebitis migrated from one region to another in the right leg and foot for a period of 6 months. About the same time the patient noted soreness in the right instep, induced by walking a few blocks, which was relieved by rest. At the time of examination the right dorsalis pedis and posterior tibial arteries were occluded, whereas those of the left foot evidenced reduced pulsations, graded 2 to 3.

The patient was seen again in 1933, having had another bout of phlebitis in both legs and arms in October, 1930, with local, burning discomfort. There had been similar recurrences at yearly intervals. When the lesions were in the feet, pain was a prominent feature. Arterial occlusion had been progressive in both legs, closing both popliteal arteries. There was claudication involving the muscles of the calf, with sharp reduction in the amount of walking the patient could do.

These episodes of phlebitis, flaring up at yearly intervals, revealed the relapsing nature of the disease. Thrombosis of the arteries seemed to parallel the phlebitis. The pain of phlebitis was disagreeable and annoying, but there were no residual symptoms when the condition was quiescent, as compared to the arterial closure that left a progressive impairment of walking.

The pain resulting from an inflammatory lesion of the vein is generally minimal. In 15 cases there was only tenderness along the course of the vein. Pain of grade 4 did not occur, and that of grade 3 occurred in only 3 cases. In cases of phlebitis, when pain was an important feature it was of a dull, aching or burning type, fairly well localized, and was at times associated with muscular soreness, stiffness, and twitching. Four patients had exacerbations of the pain with exercise, 1 of them suffering a sharp, stabbing pain that was projected peripherally with activity of the involved part that suggested periadventitial neuritis.

The pain of arteritis was only slightly more severe than that of phlebitis. It marked the onset of thrombo-angiitis obliterans in 4 cases. A tender, nodular swelling, progressing along the course of the artery, which became enlarged and pulseless, was the primary

feature. There was a generalized aching pain with coldness peripheral to the involved arterial segment. The radial, ulnar, and brachial arteries were the arteries involved in all but 1 case, in which painful arteritis of the lower femoral and popliteal arteries was present. One patient complained of cramping of the forearm and hand lasting a week; another complained of a constant, frozen, gnawing sensation, which was relieved by exercise. In 1 case of radial arteritis there was a burning, spasmodic, agonizing pain, referred to the thumb and index finger. In this case the adjacent peripheral nerve may have been involved in the inflammatory process. With the abundant nerve supply in the adventitia, it is not difficult to explain pain resulting from arterial inflammation. The surprising feature is that the pain of arteritis is so mild and is present so infrequently, as arteritis is probably present in all cases of thrombo-angiitis obliterans, although it produced symptoms in not more than 7% of our cases. The intensity and situation of the inflammatory process probably determines the presence or absence of pain. Clinical observation indicates that phlebitis of the large veins is usually less painful than phlebitis of superficial vessels, with involvement of superficial tissues. The relative infrequency of pain in the more deeply situated arteries may be explained on a similar basis.

*Acute Occlusion.* The pain of acute occlusion of a large artery is of sudden onset, with tenderness at the site of occlusion and generalized pain which is projected peripherally. There is often severe, cramping pain in the muscles. The extremity is cold, numb, cyanotic and at times swollen. The pain is usually of short duration, lasting from a few hours to several days, with gradual diminution in intensity. Movement and pressure may increase the pain, and there is often nocturnal exacerbation. The muscles are tender and the skin hyperesthetic and intermittently cyanotic, a vasospastic expression of an acute ischemic neuritis. The pain is the result of ischemia of mixed nerves and severe vasospasm. In only the most severe cases are there objective neurologic signs of neuritis. The short duration of the pain may be explained by the rapid increase of collateral circulation. This has been followed by studies of temperature. If thrombosis is not progressive, almost complete recovery of the surface temperature of the digits may occur in from 2 to 3 days. Residual hyperesthesia, numbness, tingling, and mild paroxysms of pain may be present for weeks.

**Case Report.** A man, aged 49, was seen at the Clinic in July, 1933. In September, 1931, he had suddenly experienced a moderately severe pain in the left foot and in the muscles of the calf of that leg. The left first toe and ball of the foot had been numb, and the entire lower portion of the left leg cold and cyanotic. The pain had lasted only a few days. Shortly after this, a superficial phlebitis had appeared about the right external malleolus. Since 1931 the patient had had pain in both calves after walking from one to three blocks; the pain had occurred sooner after fast walking or after walking uphill. Examination at the time of admission revealed absence of pulsations in both popliteal and distal arteries.

The first symptom of thrombo-angiitis obliterans in this case was sudden occlusion of the left popliteal artery. From then on the episodes of phlebitis and distress of claudication indicated the nature of the process. Sudden occlusion initiates the onset of thrombo-angiitis obliterans in about 10% of cases.

*Ischemic Neuritis.* Ischemic neuritis occurs relatively late in the course of thrombo-angiitis obliterans, only 3 cases having been observed in the first 18 months of the disease. Among 12% of the patients in this series this lesion developed; in 2 cases both lower extremities were involved. The neuritis was severe in 7 cases, mild in 5. The pain, in cases in which involvement was extensive, is severe, diffuse, covers large areas, and is spasmodic. It does not correspond to any definite distribution of nerves. There are sharp, shooting pains which extend from one end of the extremity to the other. The pains at times are pulling, tearing, and agonizing; at other times they are burning and throbbing. In addition to these paroxysms, there may be a constant, dull, diffuse pain which shifts from one region to another. During paroxysms the extremity may appear a mottled dark bluish-red owing to excessive vasoconstriction which is a result of the inclusion of sympathetic fibers in the neuritic lesion. With cessation of the severe pain, the color may become more nearly normal. The paroxysms of excruciating pain occur most often at night, and may last for several hours. Large doses of morphin and hyoscin, hypodermically, and alcohol by mouth, either singly or combined, may fail to give relief for more than a short time. Elevation of the extremity gave partial relief in 2 cases. Fever therapy had little effect. Rarely, pain has been so severe, constant, and intractable that amputation or chordotomy has been necessary.

Severe forms of ischemic neuritis ran a prolonged course (from 1 to 8 months) in this group of cases. The pain gradually diminished in severity and the area of distribution became less in extent.

Mild cases of ischemic neuritis are similar to those just described, although a smaller portion of the extremity is involved and the pain may follow a definite nerve distribution. One case of posterior tibial neuritis and 1 of superficial peroneal neuritis were present in this group.

The bloodvessels of the affected extremity are usually extensively involved. Of 11 cases of neuritis of the lower extremity, femoral pulsations were absent in 7, and reduced in 1. In the 3 patients with open femoral arteries the neuritis was confined to the lower part of the leg and foot.

Complete neurologic examination of the involved extremity was carried out in 6 cases: reflexes were reduced in 3 and normal in 3. There were sensory changes of marked degree in 1 case, slight changes in 3, and no changes at all in 2. The most frequent sensory change was marked hyperesthesia; the second, partial anesthesia

of the affected limb. Numbness and coldness, tingling, and other forms of paresthesia, with varying degrees of pain were the usual symptoms.

Sympathetic ganglionectomy had little influence on the occurrence of ischemic neuritis. Three patients had undergone this operation from 1 to 3 months before neuritis developed. One patient had neuritis in one leg before, in the other after, sympathectomy. The operation caused exacerbation of an existing neuritis in 1 case and partial relief of pain in another.

The pain of ischemic neuritis we believe to be the result of degenerative changes in nerves brought about by a lack of blood supply to those nerves rather than the result of actual inflammation from contiguity of diseased vessels. Woltman and Wilder, in a study of neuritis in diabetes, concluded that atherosclerosis of the nutrient vessel to a nerve played a prominent part in the production of the neuritis. Pain, paresthesia, and areflexia, without the usual sensitivity of nerve trunks, were the most important characteristics in their group of cases. The same features were predominant in the cases described here. Priestley, in 1932, demonstrated that peripheral nerves of extremities amputated for diabetic gangrene gave evidence of wallerian degeneration and fibrosis, the changes being more prominent distally and being proportional to the arteriosclerotic changes in the vessels. He suggested that the peripheral origin of the degeneration made it probable that it was dependent on ischemia. Brown, Allen and Mahorner found evidences of inflammation in nerve trunks in several cases of thrombo-angiitis obliterans. This was not the usual change in cases of ischemic neuritis.

Figures 4 and 5, from a case of thrombo-angiitis obliterans with advanced ischemic neuritis, reveal many nerve bundles with a marked loss of myelin and evidences of degeneration, whereas there is almost no evidence of inflammation or of fibrosis about the nerve. As in the reports just referred to, ischemia in this case seems to be the important factor in the production of the neuritis.

The paroxysmal character of the pain in this condition may be partly explained on the basis of vascular spasm that causes additional ischemia, since during the paroxysms the extremity is often more cold, cyanotic, and mottled than at other times. Exact parallelism of pain and changes in temperature could not be demonstrated in 1 case.

**Case Report.** A man, aged 48, American, had had his first symptoms of arterial disease in 1930 when arteritis of the right brachial artery had developed, causing cramping pains in the right forearm and hand. A nodule could be palpated in the brachial artery. Following this he had noted cramping and coldness of the hand with exercise. In 1931, intermittent claudication of the left arch and calf had developed after he had walked one block. In October, 1932, he had had acute occlusion of the right femoral artery, in Hunter's canal, with severe pain throughout the entire right leg; this pain had lasted several days and had prevented sleep. A few weeks

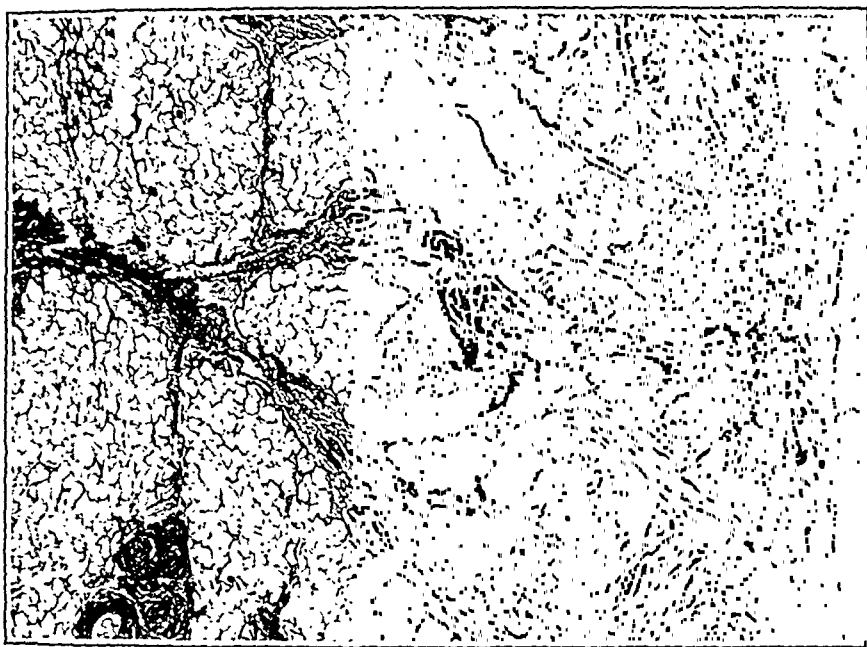


FIG. 2.—Normal skin of a digit ( $\times 30$ ).

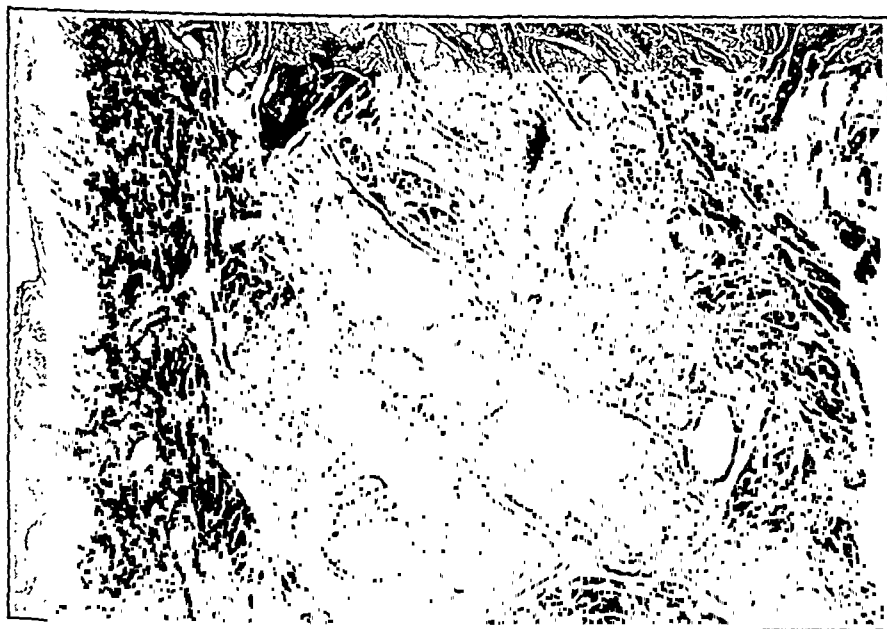


FIG. 3.—Skin of digit; thrombo-angiitis obliterans with pretrophic pain. The increase in density and amount of fibrous tissue in the corium and subcutaneous tissues, with diminution of fat and without signs of inflammation, may be noted ( $\times 30$ ).

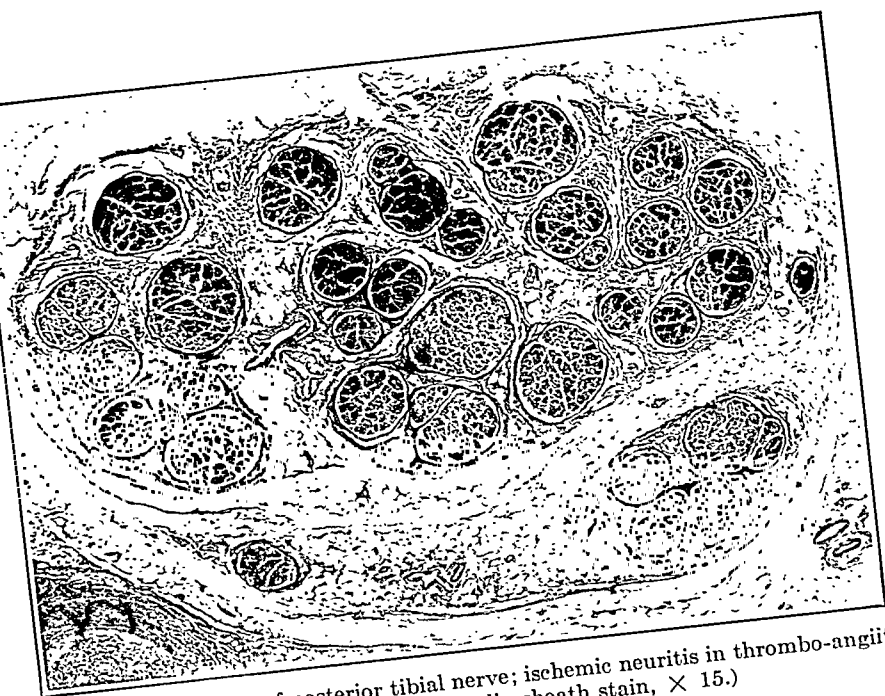


FIG. 4.—Cross section of posterior tibial nerve; ischemic neuritis in thrombo-angiitis obliterans. (Weigert's myelin sheath stain,  $\times 15$ .)

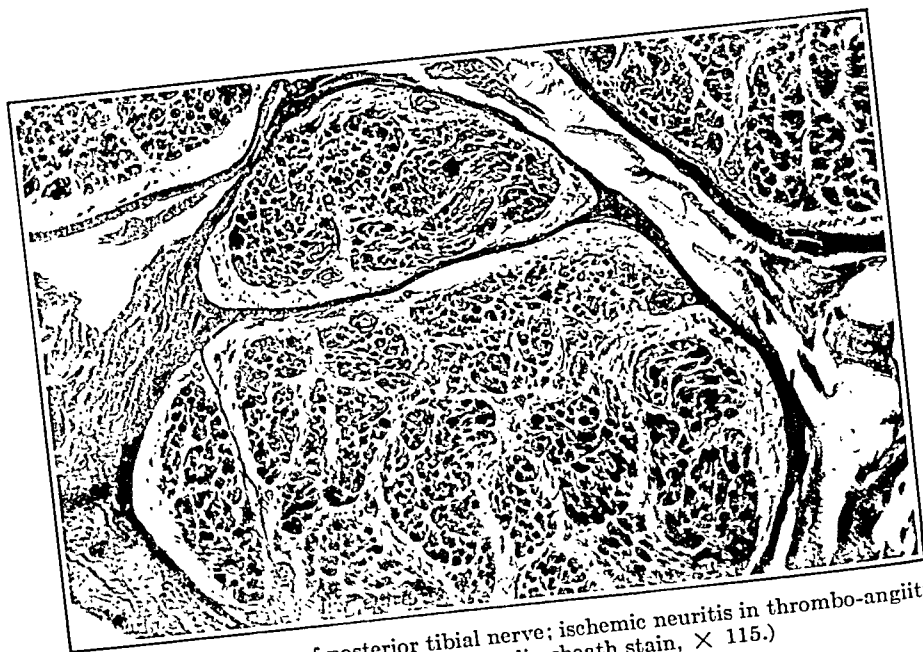


FIG. 5.—Cross section of posterior tibial nerve; ischemic neuritis in thrombo-angiitis obliterans. (Weigert's myelin sheath stain,  $\times 115$ .)

after this acute occlusion, severe rest pain had appeared in the upper part of the right leg and in the calf and foot. The pain had occurred most often at night, and had lasted 1 or more hours. The pain had been exceedingly severe, of grade 4, and had required morphin in large doses for relief. In addition to these paroxysms a constant mild pain had been present in the entire extremity, with numbness of the toes, and weakness of the muscles of the leg.

On examination there was hyperesthesia of the skin, diminished sensation to pinprick, and light touch, and tenderness of the leg below the knee. The Achilles and patellar reflexes were absent in this leg. All of the arteries of the right arm, left leg, and right leg below the mid thigh were completely occluded. The right leg was amputated in November, 1932, because of spreading gangrene.

In December, 1932, the patient had superficial phlebitis of the inner aspect of the left thigh; this spread below the knees. The left foot and left leg were swollen, suggesting that a deep phlebitis also was present. In the same month he noted severe burning, throbbing, spasmodic pain in the left leg, associated with a purple and white mottling of the left foot. The spasms lasted about an hour and were relieved somewhat by alcohol. The muscles of the foot were weak and the skin hypersensitive. In January, the patient had some cramp-like shooting pains in the left leg and foot, without vasospastic disorder. After about 9 weeks, he became free of pain until June, 1933, when superficial phlebitis of the stump of the right leg and of the left thigh developed; this was associated with edema of the left foot and leg. In July, 1933, the left first and third toes became gangrenous. Rest pain was severe and the leg was markedly hyperesthetic. The gangrene spread, necessitating amputation of the leg in July, 1933. The patient died, September 9, 1933, of coronary occlusion.

The severe forms of ischemic neuritis are more prone to develop with the rapidly progressive forms of thrombo-angiitis obliterans. The periods of remission are short, the lesion involves large arteries, and collateral circulation does not have time to develop adequately. These forms may be justly designated as fulminating, or malignant, types.

*Vasospastic Pain.* One patient noted a cramp-like pain in the muscles of the right calf, associated with a cold, white foot; the condition was relieved by nitroglycerin. Pulsations in the foot were not palpable while the pain was present but could be felt after administering a vasodilating drug. This pain seemed certainly to be of vasospastic origin, secondary to thrombo-angiitis obliterans. Usually, blanching or episodes of cyanosis, so frequently observed in this disease, do not cause pain. Sensations of numbness and aching are the usual complaints.

*Other Types of Pain.* Unclassified pain was found in 18 patients. The etiology in some cases could be surmised, in others the history was too vague and nonspecific to justify any inference as to the cause. In 2 cases the pain was probably the result of ischemia; the story was of aching pain, swelling, coldness and numbness of a digit, of several months' duration. Another patient complained of intermittent pain in the toe, accompanied by redness. This may have been a localized inflammatory process. Rest pain in the



calf of the leg, continuous for days, with occasional exacerbations relieved by heat, exercise, and change of position, was, conceivably, the result of localized arteritis or phlebitis.

**Comment.** The accessibility of the extremities for objective study has rendered the investigation of disorders of the bloodvessels particularly fascinating. The changes in pulsation in the palpable arteries allows the course of the obliterating process to be followed with great accuracy. Vasomotor disorders are obvious, exhibiting changes in color and variation in surface temperature. The evolution of trophic lesions is visible as are surface capillaries to microscopic observation. In addition to these clinical investigations, correlation with pathologic material is made possible from studies of amputated limbs or digits and of specimens at biopsy. The advent of arteriography (Allen) of the extremities by the intra-arterial injection of opaque substances, such as thorium dioxid, has made visible to an astonishing degree the distal arterial architecture, more particularly of the upper extremities. Arteriography has brought out two important factors: (1) that many male patients with disorders which were thought to be vasomotor in origin have been shown to have organic occlusion of the smaller digital arteries, and (2) that the arteries of the hands are involved in a much higher percentage of cases of thrombo-angiitis obliterans than was previously believed. It is apparent that occlusion of the arteries may occur in the face of complete absence of any signs or symptoms, indicating rapid development of collateral circulation. This is particularly true in the upper extremities.

There are two major types of pain in cases of thrombo-angiitis obliterans; (1) that resulting from ischemia of the nerves of the skin, or of the larger nerve trunks, or ischemia of the muscles, each of which causes a recognizable type of distress, and (2) that resulting from inflammation of the veins, of the arteries, or of the cutaneous tissues. This grouping holds true not only in cases of thrombo-angiitis obliterans, but also in those of other occlusive diseases of the arteries, such as arteriosclerosis, or occlusion from embolism. In arteriosclerotic disease, with the exception of that attributable to superficial phlebitis and arteritis, the same types of pain are observed as in thrombo-angiitis obliterans.

Ischemic episodes, with blanching or cyanosis of the skin, do not cause severe pain. Similar absence of significant degrees of pain occurs in Raynaud's disease, a primary vasospastic disorder. The complaint is usually a feeling of numbness or aching.

Ischemia of the larger nerve trunks causes true, ischemic degenerative changes in the nerve fibers. Actually this is not true neuritis, as only occasionally is an inflammatory process present. The pain of ischemic neuritis is fairly characteristic in that it appears with rest, occurs in the absence of trophic lesions, and usually follows sudden closure of one of the larger arteries of the limbs. The

vasospastic changes in color that accompany this are secondary manifestations of involvement of sympathetic fibers in the mixed nerve trunk.

Ischemia produces no pain in the resting muscle; pain occurs only with exercise, and this pain is known as claudication. This symptom, which comes after a constant amount of muscular activity, is thought by Lewis to be attributable to the accumulation of some "X" substance which is capable of producing pain.

Pain resulting from inflammation of the arteries and veins is not severe and is usually self-limited; it exists for a period of from 2 to 3 weeks, the time for the subsidence of the inflammatory lesion.

It is interesting to speculate as to why arteritis does not produce more serious degrees of pain. In only a small percentage of cases is arteritis painful. When present, the pain is never severe, and in the majority of cases inflammatory lesions of the arteries are unrecognizable as far as the local inflammatory process is concerned.

Pain, in older subjects with occlusive arteriosclerotic disease, is less intense, as a rule, than that observed in cases of thrombo-angiitis obliterans. Ischemic neuritis is probably of equal frequency in both arteriosclerotic disease and thrombo-angiitis obliterans. In the former, trophic lesions as a rule are less intense unless diabetes is present. With diabetes, the ulcers are usually of the moist variety, with marked degrees of secondary infection. The process, however, is primarily thrombosis resulting from arteriosclerosis. Diabetes simply modifies the type and course of the inflammation of ischemic tissues.

The individual sensitivity of the patient to painful lesions of peripheral arterial disease varies greatly, and modifies the clinical symptoms to a considerable degree. It is amazing the amount of pain a stolid individual will endure, as compared with the relatively small degrees of pain that a highly sensitive subject can tolerate. These individual differences in sensitivity are particularly important from the standpoint of treatment. Amputation or radical neurologic procedures may be imperative because of the low threshold for pain which causes a breaking of the morale of a hypersensitive person.

An interesting group of patients have been observed who have advanced grades of closure of the arteries and ulcers of the digits but with complete absence of pain. This cannot entirely be explained on the basis of lowered sensitivity of the individual to pain, and it has occurred among patients without demonstrable evidence of neuritis. Pathologic studies of the amputated extremities of these patients have thrown no light on these paradoxical findings.

Differentiation of the types of pain in cases of occlusive disease of the bloodvessels assumes importance from the standpoint of treatment. The relief of pain is a paramount problem. Often on its control depend preservation of the morale of the patient and preservation of the limbs. As recognition of the basis of the pain

has advanced, so has more effective therapy. The newer tissue extracts (Roth) used in treatment of the pain of claudication have given increased range of activity in a high percentage of cases. More effective control of the pain resulting from ulcers and gangrene has been obtained by rest, by immersion of the affected parts in mild non-irritating solutions, such as boric acid, by the use of anesthetic solutions locally, by induction of fever by foreign proteins, and occasionally by section of the sensory branches of the peripheral nerves. Sympathetic ganglionectomy is not carried out for the relief of pain, but has a definite field of usefulness in the prevention of recurrent ulcers. The pain of phlebitis and arteritis frequently can be controlled by the use of Roentgen therapy. The control of the pain of ischemic neuritis is at present a major problem. No entirely effective treatment is available. The milder forms are self-limiting and can be controlled with mild analgesic drugs, or alcohol by mouth, and treatment with Roentgen rays over the lumbar portion of the spinal column. In the severe forms of neuritis control of pain may be often impossible and operative measures may be necessary; in several cases chordotomy has been performed.

**Summary.** There are 7 distinct recognizable types of pain in thrombo-angiitis obliterans. The two major factors involved in the production of pain are: (1) ischemia, and (2) inflammation. The types of pain observed in arteriosclerosis obliterans are similar to those in thrombo-angiitis obliterans, with the exception that pain resulting from phlebitis and arteritis is absent.

Intermittent claudication was the initial symptom in more than 90% of the cases in this series. The recognition of the arterial basis of this symptom is of crucial importance, as avoidance of ulcers and gangrene and preservation of limbs depend largely on early appreciation of the circulatory impairment. The presence or absence of pulsations in the peripheral arteries should be determined in any case in which pain in the extremities is a prominent feature.

All types of pain present in this disease are amenable to treatment with the exception of that attributable to severe degrees of ischemic neuritis.

The decrease in the incidence of amputation in cases of thrombo-angiitis obliterans has followed, to a large degree, the effective treatment of pain.

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## THE FOUR-LEAD ELECTROCARDIOGRAM IN CORONARY SCLEROSIS.

### A STUDY OF A SERIES OF CONSECUTIVE PATIENTS.\*

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It is becoming more apparent that the electrocardiogram is an important element in evaluating the condition of the coronary circulation. Its place in the diagnosis of recent coronary occlusion is well established but its use in other forms of coronary insufficiency is still not fully appreciated. It is known that serial electrocardiograms over a long period of time in patients with coronary sclerosis frequently show slowly progressive changes in the conventional 3 leads, which have been ascribed to the myocardial changes resulting from the progressive coronary sclerosis.<sup>1,2,3</sup> Since the precordial lead has been shown to be so definite an aid in the diagnosis of recent coronary occlusion,<sup>2,4,5,6</sup> it seemed to us reasonable to suppose that it might also afford some information as to the progress and degree of myocardial damage resulting from coronary sclerosis. Information concerning the extent of the myocardial damage and the degree of coronary insufficiency present obtained at an early period, it seems to us, is of far greater value to the clinician than evidence as to the localization of the myocardial lesion obtained

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later after an occlusion has finally occurred. In fact, in most instances where patients with recent coronary occlusion have come to autopsy, the hearts have been found to show definite coronary sclerosis often associated with extensive myocardial fibrosis and infarcts of long standing which were thought to have contributed to the earlier clinical disability.<sup>3</sup> With this in view we have undertaken a study of the 4-lead electrocardiogram in a large series of patients with coronary sclerosis diagnosed clinically.

**Procedure.** 1. *Technique of Taking Lead IV.* The method used for taking the 4th lead was similar to that described by Wolferth and Wood.<sup>4</sup> This was chosen because considerable data have already been assembled with this particular method, so that it has become conventional and comparisons with previous work would, therefore, be more intelligible. The procedure established by Katz and Kissin<sup>5</sup> was followed with some modification. In brief, with the patient on his back, one of the standard (2½ by 5 cm.) tin electrodes was applied at the level of the 4th interspace, a little to the left of the sternum and attached to the right arm terminal, and the other electrode was placed on the posterior chest wall or on the left leg and attached to the left arm terminal. Care was taken to insure a close application of electrodes, to keep the skin resistance low, and to prevent overshooting. The curves obtained using the left leg as the point of lead off were similar to those using the posterior chest wall (Wolferth and Wood<sup>4</sup>). Wilson<sup>7</sup> has clearly shown that the location of the anterior precordial electrode is far more important than that of the other. We feel that it is advisable for convenience to place the posterior lead on the leg in all patients; this is our practice at present. This combination we have designated throughout this report as Lead IV. The use of the 4th interspace just to the left of the sternum was selected as the place for the electrode because it is an easily ascertainable and fixed point for use in taking serial records and for comparison among different individuals. This does not apply to the point of the maximum apex beat used by Wolferth and Wood<sup>4</sup> and others. The 4th interspace is over the heart, and is less influenced by the position of the diaphragm than the 5th interspace which is used by some other workers. In normal persons, records obtained with the anterior electrode in the 4th interspace show a practically constant electrocardiographic contour in successive curves.

It has been suggested that the precordial electrode be connected to the left arm terminal instead of the right. If this were done the exact inverse image of the curves here described would be obtained with the phase signs of positive and negative reversed. It would be unfortunate, in our opinion, to confuse the issue by such reversal from the established practice, particularly since the direction of deflections is purely arbitrary and the present curves have gained wide use. Unless real justification is given for reversing the curves, we propose to continue with the present method.

2. *Method of Selecting Patients.* For a time during 1932, Lead IV was taken routinely on all patients over 40 years regardless of diagnosis. Since then it has been taken on all patients on whom a clinical diagnosis of coronary sclerosis, angina pectoris, arteriosclerosis or hypertension had been made or suspected.\* In this manner a large mass of electrocardiographic material was assembled.

After having obtained these records, the available clinical histories of the patients were carefully analyzed independently of the electrocardio-

\* This was in addition to the patients with suspected recent coronary occlusion (cf. Katz and Bohning<sup>3</sup>).

graphic findings. On the basis of the clinical findings alone, a separation of these patients was made into three groups.

Group I, Series A, consisted of 100 patients with clinical findings definitely indicating moderate or advanced coronary sclerosis. The common clinical findings in this group were dyspnea on exertion and precordial pain associated with heart muscle weakness, peripheral arteriosclerosis or a widened aorta. During the preparation of this report a second series of electrocardiograms from 100 patients diagnosed clinically as coronary sclerosis was collected and analyzed. This we have designated Group I, Series B.

Group II consisted of 50 patients in whom coronary sclerosis was at some time suspected, but whose clinical picture was not definite enough to diagnose moderate or advanced coronary sclerosis with certainty or in whom the symptoms could have been caused by another condition.\* Groups I and II included both hospital and ambulatory patients.

Group III (added as a control) consisted of 100 patients falling within the required age group, but whose clinical diagnosis was unknown to us. They were ambulatory patients referred for electrocardiograms by physicians from among their private patients. They were all, however, under suspicion of some cardiac involvement and, although the nature of this was undesignated, a fairly varied group of cardiac abnormalities was probably included.

In addition, as a further control we obtained 4-lead electrocardiograms on a group of 25 normal subjects, interns and technicians, and on a group of 133 patients known to have other types of organic heart disease.

In 56 patients of Group I, where a definite diagnosis of coronary sclerosis had been made, repeat 4-lead tracings were obtained at intervals covering from 4 months to more than 2 years.

**Results.** After separating the records of the patients into the groups outlined above, the electrocardiographic findings of each group were carefully analyzed to determine the frequency of abnormalities. The abnormalities in Lead IV were then studied in detail, classified and correlated with the findings in the other three leads, with the clinical findings and, in the few autopsied cases, with the autopsy findings. For this purpose several extensive correlation tables were assembled from which sundry summary tables were made. In addition the value of the repeated records was estimated.

1. *Frequency of Abnormal and Normal Electrocardiograms in the Several Groups.* The criteria used for the normal Lead IV were those established by the studies of Wolferth and Wood,<sup>4</sup> Katz and Kissin,<sup>5</sup> Masters,<sup>9</sup> Goldbloom<sup>10</sup> and by the analysis of the 25 normal subjects used as controls in this study (Table 1). It can be seen that the various investigators agree rather closely as to the normal limits and our own findings agree fairly well with those of others. From these data the criteria to be used in differentiating a normal from an abnormal Lead IV were determined (Table 2). Variations in the P wave were disregarded for the most part as being of little importance. In classifying the standard 3 leads the usual criteria we employ for normality were used (Katz and Johnson<sup>11</sup>).

\* Patients with cardiovascular syphilis were excluded from these two groups. In a small series of patients with syphilis, 21 in all, 50% had an abnormal Lead IV.

TABLE 1.—NORMAL VARIATIONS IN AMPLITUDE IN LEAD IV, EXPRESSED IN MILLIMETERS.

Investigator.	No. of cases.	P wave.		Primary negative portion of Q-R-S or Q wave.		Positive portion of Q-R-S.		Total amplitude of Q-R-S.		S-T segment.		T' wave.	
		Aver.	Range.	Aver.	Range.	Aver.	Range.	Aver.	Range.	Aver.	Range.	Aver.	Range.
Katz and Kissin <sup>5</sup>	25	-0.8	+0.5 to -1.5	-8.5	-1.0 to -19.0	+12.0	+2.0 to +33.0	20.0	5.0 to 34.0	-1.0	0.0 to -2.0	-3.0	+1.0 to -8.0
Masters <sup>7</sup>	104	-0.8	+2.0 to -2.0	-5.3	-1.5 to -14.0	+10.7	+2.5 to +26.0	..	..	-1.0	0.0 to -2.0	-3.3	-1.0 to -7.5
Goldbloom <sup>10</sup>	25	-0.6	+1.0 to -2.0	-7.2	-3.0 to -14.0	+10.8	+6.0 to +15.0	..	..	..	..	-4.9	-2.0 to -8.0
Bohning and Katz	25	-0.3	+1.0 to -1.0	-7.9	-2.0 to -15.0	+15.0	+6.5 to +24.5	25.1	13.0 to 39.0	-1.3	-0.5 to -2.0	-5.7	-2.0 to -10.0
Total No. records measured	179	-0.6	+2.0 to -2.0	-7.2	-1.0 to -19.0	+12.1	+2.0 to +33.0	22.5	5.0 to 39.0	-1.1	0.0 to -2.0	-4.2	+1.0 to -10.0

NOTE.—In addition Wolferth and Wood,<sup>4</sup> Lieberman and Liberson,<sup>24</sup> Hoffman and Delong<sup>13</sup> have described similar normal types without reporting actual measurements. Their method of applying the electrodes was essentially the same as ours with the anterior electrode near the lower end of the sternum or at the apex and attached to the right arm terminal. Most cases were taken with the posterior electrode on the back and attached to the left arm terminal. Our cases, however, were all taken on the left leg, which, as we have pointed out in the text, gives essentially the same type of curve.

TABLE 2.—CRITERIA FOR NORMAL LEAD IV AND ABNORMAL VARIATIONS IN LEAD IV.

Record.	T wave.	Q wave or primary negative portion of Q-R-S complex.	Direction of main deflection of Q-R-S complex.	S-T segment.	T wave.
Normal	Negative or diphasic	Always present and usually deep	Diphasic or essentially so (1st deflection neg.)	Occasionally isoelectric, but usually neg. (less than -2 mm.)	Negative (less than -8 mm.).*
Abnormal	1. Isoelectric 2. Positive 3. Polyphasic	1. Very small 2. Absent	1. Entirely pos. (monophasic) 2. Mainly pos. (diphasic) with small neg. 1st deflection 3. Mainly pos. (diphasic) with small neg. end deflection 4. Entirely neg. (monophasic) 5. Mainly neg. (diphasic) with small pos. end deflection 6. Mainly neg. (diphasic) with small pos. 1st deflection 7. Triphasic—W or M types 8. Polyphasic 9. Unusually large 10. Unusually small	1. Neg. (-2 mm. or more) 2. Pos. of any degree	1. Deeply neg. (-8 mm. or more). 2. Barely discernible or flat and isoelectric. 3. Positive. 4. Diphasic, with 1st phase neg. 5. Diphasic, with 1st phase pos. 6. Polyphasic.

\* With electrode in the fourth interspace to left of sternum.

The frequency of normal and abnormal electrocardiographic findings in the 3 groups of patients is assembled in Table 3. It can be readily seen that Group I shows a much higher percentage of abnormality in Lead IV and in the conventional 3 leads than is found in either of the other 2 groups. Lead IV showed abnormality most often when the conventional 3 leads were also abnormal. Only 3% of Group I, 8% of Group II and 6% of Group III had normal conventional 3 leads and an abnormal Lead IV. More often a normal Lead IV was present in association with abnormality in the standard 3 leads. This occurred in Group I in 26% of all patients, in Group II in 40% and in Group III in 36%.

TABLE 3.—A COMPARISON OF THE INCIDENCE OF ABNORMALITY IN LEAD IV WITH THAT IN LEADS I, II AND III.

Clinical grouping.	Group I.		Group II.	Group III.
	Series A.	Series B.		
Diagnosis . . . . .	Coronary sclerosis	Coronary sclerosis	Suspected coronary disease	Undesignated (control group.)
Clinical findings . . . . .	Definite	Definite	Indefinite	Unknown.
Total number of patients . . . . .	100	100	50	100
Range of ages, yrs. . . . .	40. to 87	36 to 75	30 to 75	35 to 78
Average age, yrs. . . . .	59	56	52	54
Lead IV, abnormal . . . . .	69% *	68%	24%	32%
Leads I, II, III, abnormal . . . . .	92%	83%	56%	62%
Leads, I, II, III, IV, all abnormal . . . . .	66%	65%	16%	26%
Leads I, II, III, normal; Lead IV, abnormal . . . . .	3%	3%	8%	6%
Leads I, II, III, abnormal; Lead IV normal . . . . .	26%	18%	40%	36%

The presence of abnormality in Lead IV in 68.5% of our series of 200 patients with coronary disease is larger than that reported by Goldbloom,<sup>10</sup> who found an abnormal Lead IV in 37.5% of his series of 40 patients with coronary sclerosis. This variation is due largely to the difference in criteria used to establish abnormality of this lead. Goldbloom does not regard a negative  $T_4$  of 9 mm. as abnormal, although from Table 1 it can be seen that only 1 instance of a normal subject out of 179 has yet been reported with a  $T_4$  of 9 mm. or more. Recently, Wood *et al.*<sup>6</sup> found that occasion-



ally  $T_4$  was larger than 9 mm. in their series of normal subjects—but they placed their precordial electrode over the apex. Goldbloom does not interpret a diphasic  $T_4$  as abnormal as we, and most others, do. But most important of all he entirely ignores the  $S$ - $T_4$  deviations, which we and others consider as one of the variations most significant of abnormality. Two mm. was the upper limit of  $S$ - $T$  negativity in normal subjects reported in Table 1 and a positive  $S$ - $T$  segment was never found in these normal subjects.

The records of a group of 133 instances of patients with organic heart disease of miscellaneous origins were also examined. While similar changes appeared in some of them, the frequency was about one-half that of the 200 cases of coronary sclerosis, and the abnormalities of Lead IV were much less than those found in our series of coronary sclerosis.

While we found that Lead IV alone was diagnostically characteristic in only a few instances when the standard 3 leads were normal, nevertheless Lead IV was of very definite assistance in aiding in the determination of the extent of myocardial damage in many patients. Abnormalities when present in Lead IV are usually striking in appearance and, for this reason, often served as a final clue in evaluating a record which might otherwise be doubtful, if judged by the conventional 3 leads alone. However, just as in the standard leads, different degrees of abnormalities were found varying from the borderline of normality to unquestionable deviations from the normal. Furthermore, greater significance was attached to an abnormality when it occurred associated with other abnormalities, whether in the 4th or the other leads.

2. *Relation of Abnormal Lead IV to the Clinical Findings in the 100 Patients With Coronary Sclerosis (Group I, Series A).* The data of this correlation are assembled in Table 4. The patients were divided into 2 groups, those with normal and those with abnormal Lead IV. It will be seen that dyspnea on exertion and palpitation, cardiac enlargement, edema and congestive heart failure were more frequent in the group with abnormal Lead IV. Furthermore, digitalis therapy was more often required in this group. Pain referable to the heart was present in 85% of all patients, but was only slightly more frequent in the group with abnormal Lead IV. Arteriosclerosis of some type, including peripheral and aortic, was present in 93% of all patients and was about equally distributed between the 2 groups. Hypertension, interestingly enough, was found more frequently in the group with normal Lead IV. The significance of this finding is not clear. In a considerable number of patients a high blood pressure present years earlier had become definitely lower after clinical symptoms of heart muscle weakness had become apparent.

The increased frequency of the finding of dyspnea, palpitation, edema, cardiac failure and cardiac enlargement in patients with

abnormal Lead IV does seem to indicate that these patients had a relatively greater degree of myocardial damage than the group with normal Lead IV. This observation lends support to the view that the appearance of Lead IV is determined by the presence of advanced myocardial involvement and, therefore, can be used as one sign of the presence of this condition.

TABLE 4.—RELATION OF ABNORMALITY IN LEAD IV TO THE CLINICAL FINDINGS IN THE 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

Clinical findings.	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
Sex:			
Male . . . . .	61	51	54
Female . . . . .	39	49	46
Complaints:			
Dyspnea on exertion . . . . .	48	65	60
Palpitation . . . . .	22	35	31
Pain, all types . . . . .	80	87	85
Pain, precordial . . . . .	77	84	82
Pain, substernal . . . . .	6	8	8
Pain, radiating to arm . . . . .	29	19	22
Pain, epigastric . . . . .	0	3	2
Physical findings:			
Hypertension . . . . .	76	53	60
Systolic blood pressure:			
Under 100 . . . . .	0	1	1
100 to 150 . . . . .	21	46	39
150 to 180 . . . . .	42	19	26
180 to 200 . . . . .	13	12	12
Over 200 . . . . .	21	22	22
Arteriosclerosis . . . . .	90	94	93
Cardiac enlargement . . . . .	48	61	57
Distant heart tones . . . . .	42	43	43
Systolic murmurs . . . . .	45	40	42
Diastolic murmurs . . . . .	3	7	6
Edema . . . . .	6	21	17
Heart failure of some degree . . . . .	22	33	30
Cyanosis . . . . .	9	4	6
Digitalis therapy employed . . . . .	6	32	24

3. *Relation of Abnormal Lead IV to the Occurrence of Abnormalities in the Standard 3 Leads in the 100 Patients With Coronary Sclerosis (Group I, Series A).* A further estimate of the value of Lead IV can be obtained by comparing the appearance of the standard 3-lead electrocardiogram when this lead is normal and when it is abnormal. This comparison has been summarized in Table 5. The terms used have been those employed by us in interpreting electrocardiograms (Katz and Johnson<sup>11</sup>). It will be seen that the standard 3 leads were not only somewhat more frequently abnormal in the patients with abnormal Lead IV, but the degree of abnormality of the curves was greater, as indicated by the interpretations, "compatible with," "suggests" and "indicates myocardial involvement." The details as to specific aberrations of the several complexes are clearly to be seen in Table 6. Extrasystolic arrhythmias were more frequent in patients with abnormal Lead IV than in

those with this lead normal, and intraventricular and *A-V* block were not encountered when the 4th lead was normal. There can be no doubt that abnormalities in Lead IV are not only associated more frequently with clinical evidence of myocardial damage, but also with electrocardiographic evidence of such damage in the standard 3 leads. An abnormal Lead IV, this evidence would also suggest, is an additional clue to the electrocardiographic diagnosis of myocardial dosage.

TABLE 5.—RELATION OF ABNORMALITY IN LEAD IV TO THE OCCURRENCE OF ELECTROCARDIOGRAPHIC DEVIATIONS IN THE STANDARD THREE LEADS IN THE 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

Type of deviation.	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
Leads I, II, III, abnormal . . . . .	84	96	92
Myocardial involvement:			
Compatible . . . . .	16	4	8
Suggested . . . . .	19	12	14
Indicated . . . . .	49	80	70
Extrasystoles . . . . .	3	13	10
Auricular fibrillation . . . . .	3	4	4
Block:			
Intraventricular . . . . .	0	11	8
Complete <i>A-V</i> . . . . .	0	1	1
Partial <i>A-V</i> . . . . .	0	1	1
<i>Q-R-S</i> deviations:			
Slurring . . . . .	100	100	100
Notching of <i>Q-R-S</i> <sub>1</sub> . . . . .	0	8	6
Notching of <i>Q-R-S</i> <sub>2</sub> . . . . .	3	11	9
Notching of <i>Q-R-S</i> <sub>3</sub> . . . . .	9	39	30
Left axis shift . . . . .	48	47	47
Left ventricular preponderance . . . . .	22	30	28
Right ventricular preponderance . . . . .	0	3	2
Low "voltage" (standard 3 leads) . . . . .	6	11	10
<i>S-T</i> deviations:			
Negative <i>S-T</i> <sub>1</sub> . . . . .	35	43	41
Negative <i>S-T</i> <sub>2</sub> . . . . .	25	58	34
Negative <i>S-T</i> <sub>3</sub> . . . . .	0	13	9
Positive <i>S-T</i> <sub>1</sub> . . . . .	0	8	6
Positive <i>S-T</i> <sub>2</sub> . . . . .	0	11	8
Positive <i>S-T</i> <sub>3</sub> . . . . .	12	26	22
<i>T</i> deviations:			
Negative <i>T</i> <sub>1</sub> . . . . .	0	20	14
Negative <i>T</i> <sub>2</sub> . . . . .	3	15	11
Negative <i>T</i> <sub>3</sub> . . . . .	32	35	34
Diphasic <i>T</i> <sub>1</sub> . . . . .	13	19	17
Diphasic <i>T</i> <sub>2</sub> . . . . .	3	16	12
Diphasic <i>T</i> <sub>3</sub> . . . . .	10	19	16

4. *The Abnormalities in Lead IV Encountered in the 100 Patients With Coronary Sclerosis (Group I, Series A).* An attempt was made to see if the changes in Lead IV could be divided into several groups. For this purpose the direction and magnitude of the deviation of the various complexes were determined as shown in Table 6. The separation of the group into those with normal and those with

abnormal Lead IV serves to emphasize the criteria used to establish whether the lead was to be classified as normal or abnormal.

TABLE 6.—VARIATIONS IN THE COMPLEXES ENCOUNTERED IN LEAD IV IN THE 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

Complex and type of deviation	Per cent of all cases with		
	Normal Lead IV.	Abnormal Lead IV.	Coronary sclerosis.
<i>P</i> <sub>4</sub> :			
Positive . . . . .	3	8	7
Negative . . . . .	68	52	60
Isoelectric . . . . .	29	50	33
<i>Q</i> <sub>4</sub> or primary negative portion of <i>Q-R-S</i> <sub>4</sub> :			
Absent . . . . .	0	10	7
Small (negative) . . . . .	0	53	36
Medium (negative) . . . . .	78	14	34
Deep (negative) . . . . .	22	23	23
Main deflection of <i>Q-R-S</i> <sub>4</sub> :			
Monophasic positive . . . . .	0	7	5
Mainly positive . . . . .	0	54	37
Diphasic . . . . .	100	23	47
First deflection positive and small . . . . .	0	3	2
Mainly negative . . . . .	0	4	3
Monophasic negative . . . . .	0	9	6
<i>S-T</i> <sub>4</sub> :			
Positive . . . . .	0	7	5
Isoelectric . . . . .	29	13	18
Negative . . . . .	71	80	77
Less than -1 mm. . . . .	42	28	32
-1 to -2 mm. . . . .	29	31	30
-2 to -4 mm. . . . .	0	13	9
-4 to -7.5 mm. . . . .	0	8	6
<i>T</i> <sub>4</sub> :			
Positive . . . . .	0	10	7
Diphasic . . . . .	0	22	15
Negative . . . . .	100	68	78
-1 to -3 mm. . . . .	29	14	19
-3 to -5 mm. . . . .	32	16	21
-5 to -8 mm. . . . .	29	25	26
-8 to -11 mm. . . . .	10	13	12

With this as a background we next classified the records according to the form of the *Q-R-S* and *T* complexes encountered in Lead IV. In Table 7 is tabulated the appearance of the other phases of the ventricular complex encountered in each of the *Q-R-S* and in each of the *T* types. It is interesting that the second series (B) of 100 cases of coronary sclerosis had a similar distribution.

From this material we next attempted to describe the commoner types of Lead IV seen. This has not been an easy task because of the overlapping and the finer gradations as a survey of Table 7 will show. However, we feel that it is fair to say that 4 main types of abnormality in Lead IV are encountered in coronary sclerosis. We have designated these as (1) the positive *Q-R-S*<sub>4</sub> type (the most common), (2) the negative *Q-R-S*<sub>4</sub> type, (3) the positive and diphasic *T*<sub>4</sub> type and (4) the deeply negative *T*<sub>4</sub> type. Naturally there is some overlapping between the groups as one of the *Q-R-S* types

TABLE 7.—TABULATION OF ABNORMALITIES FOUND IN LEAD IV IN 100 PATIENTS WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

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TABLE 7.—TABULATION OF ABNORMALITIES FOUND IN LEAD I  
WITH CORONARY SCLEROSIS (GROUP I—SERIES A).

		Associated findings in the ventricular complex in Lead IV.													
		Q wave.*		S-T deviation.		T wave.									
						Di-phasic.		Negative.							
										Intraventricular block (Q-R-S prolonged).					
No.	Absent.	Present.	Positive.	Isoclectric	-2 mm. or less.	More than -2 mm.	Positive	1st phase positive.	1st phase negative.	Less than -8 mm.	-8 mm. or more.				
I on the basis of the form of Q-R-S <sub>1</sub>	Q-R-S <sub>1</sub> positive	Entirely pos. Mainly pos.	5 37	5 0	0 37	0 0	0 2	25 10	1 0	0 0	1 1	0 30	3 6	2 1	
Q-R-S <sub>1</sub> diphasic	1st deflection neg.†	Total	42	5	37	0	2	27	13	1	0	2	30	9	3
Q-R-S <sub>1</sub> negative	Entirely neg. Mainly neg., 1st phase neg. Mainly neg., 1st phase pos.	1st deflection neg.†	16	0	16	1	4	10	1	3	2	8	2	1	1
Q-R-S <sub>1</sub> negative	Total	Entirely neg. Mainly neg., 1st phase neg. Mainly neg., 1st phase pos.	6 3 2	0 0 2†	6 3 0	3 1 0	2 1 0	1 1 2	0 0 0	2 0 0	2 0 1	0 1 0	2 1 1	0 0 0	3 0 2
II on the basis of the form of T <sub>1</sub>	T <sub>1</sub> positive	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	1 3 2	1 0 0	0 3 2	0 0 1	0 0 1	0 0 0	1 0 0	1 3 2	..	..	..	..	0 0 2
T <sub>1</sub> diphasic 1st phase negative	Total	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	2 8 1	1 0 0	1 8 1	0 0 1	0 0 0	2 7 0	0 1 0	..	0 0 0	2 8 1	..	..	0 1 0
T <sub>1</sub> diphasic 1st phase positive	Total	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	0 2 3	0 0 1†	0 2 2	0 1 2	0 1 0	0 0 1	0 0 0	..	0 2 3	0 0 0	..	..	0 0 2
T <sub>1</sub> negative	Total	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	5	1	4	3	1	1	0	..	5	0	..	..	2
Grand total	T <sub>1</sub> diphasic both types	Total	16	2	14	4	1	10	1	..	5	11	..	..	3
T <sub>1</sub> negative	Total	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	39 3 5	3 0 1†	36 3 4	0 0 0	2 0 2	24 3 3	13 0 0	..	..	..	30 2 5	9 1 0	3 0 1
T <sub>1</sub> negative	Total	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	47	4	43	0	4	30	13	..	..	..	37	10	4
Grand total	Total	Q-R-S <sub>1</sub> mainly pos. Q-R-S <sub>1</sub> diphasic, 1st ph. neg. Q-R-S <sub>1</sub> mainly neg.	69	7	62	5	9	41	14	6	5	11	37	10	9

\* First negative portion of Q-R-S<sub>1</sub>.  
† No instance was found with 1st phase positive.  
‡ First deflection of Q-R-S<sub>1</sub> complex is positive.

may be associated with one of the *T* types. The criteria by which each type is classified and the appearance of the other phases of the ventricular complex encountered are summarized in Table 8 and are illustrated in Figs. 1 to 17.

TABLE 8.—SUMMARY OF THE MOST COMMON ABNORMAL TYPES OF LEAD IV FOUND IN 200 PATIENTS WITH CORONARY SCLEROSIS.

	No. found	Associated findings in other phases of ventricular complex.				Remarks.	Illustrated in Fig.
		Q wave or primary negative portion of <i>Q-R-S</i> .	Main direction of <i>Q-R-S</i> complex.	<i>S-T</i> segment.	<i>T</i> wave.		
(1) <i>Q-R-S</i> , positive type	83	Absent or small	Entirely or mainly pos.	Usually neg. and ranges from $-1$ to $-8$ mm.	Usually neg.; mod. to deep (occ. diphasic and rarely pos.)	Most common type (assoc. with E.C.G. evidence of myocardial involvement in standard leads)	3 4 5 7 8 9 10 12
(2) <i>Q-R-S</i> , negative type	16	Usually present and deep	Entirely or mainly neg. (sometimes a small pos. deflection precedes main neg. deflection)	Varies—may be pos., isoelectric or neg.	Varies—most often neg., more rarely pos. or diphasic with 1st phase neg.	Not so common (often associated with intraventricular block)	6 14 15 A, B 16 A, B
(3) <i>T</i> , positive or diphasic type	50	Usually present and small, may be absent	Varies—frequently diphasic, but may be pos. or neg.	Varies—usually neg. but may be isoelectric or pos.	Pos. or diphasic (usually of type having 1st phase neg.)	Resembling the type with ant. wall infarction, as seen in recent coronary occlusion	5 7 8 9 10A 13C 15B 16 A, B
(4) <i>T</i> , deeply negative type	14	Usually present; may be mod. deep or absent	Usually mainly pos.; often diphasic	Neg.; often deeply neg.	Deeply neg. ( $-8$ to $-15$ mm.)	Resembling the type with post. wall infarction, as seen in recent coronary occlusion	11

In the *positive Q-R-S<sub>4</sub> type*, which occurred 83 times in the 200 cases, the *Q-R-S* complex was mainly or entirely positive (Figs. 3, 4, 5, 7, 8, 9, 10, 12). The former was the more usual form, the *Q* wave or primary negative portion of *Q-R-S* being present, but small. In 7 instances the *Q-R-S* complex was entirely positive (Figs. 8, 9). At times a *W* form was seen (Fig. 5). The *S-T* segment was usually within normal limits (Figs. 3, 5, 10, 12) but in 20 records was definitely negative (Figs. 4, 7, 8, 9). The *T* wave was usually within normal limits (Figs. 3, 4, 10 B, 12 A, B, C), but once was positive (Fig. 5), 15 times diphasic (Figs. 7, 8, 9, 10 A) and 11 times deeply negative. This positive *Q-R-S<sub>4</sub>* type was found in patients with intraventricular block only 6 times.

In the *negative Q-R-S<sub>4</sub> type*, which occurred 16 times in 200 cases, the *Q-R-S* complex was mainly or entirely negative (Figs. 6, 14, 15, 16). In 6 instances the *Q-R-S* complex was entirely negative

(Figs. 14 *B*, 15 *B*). In 8 the complex was diphasic, with the 1st phase negative (a deep *Q*) (Figs. 14 *A*, 15 *A*). In the other 2 the 1st phase was small and positive (Fig. 16 *A*, *B*). At times an *M* form was seen (Figs. 6, 14 *B*) or a *W* form (Fig. 15 *B*, *C*). The

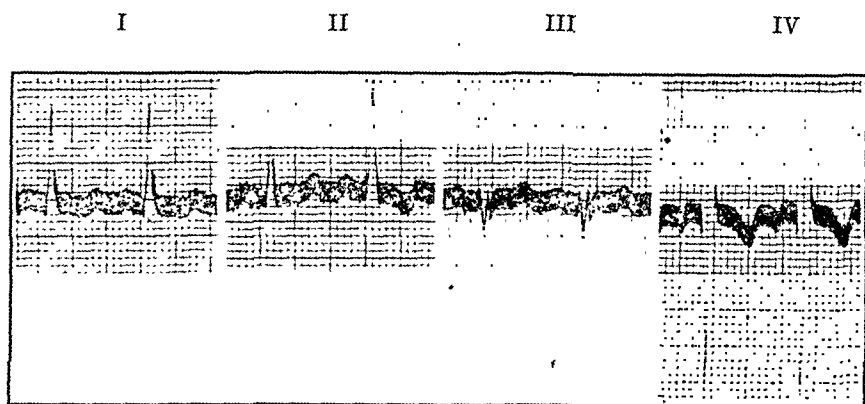


FIG. 1.—Moderate coronary sclerosis, moderate myocardial fibrosis and fatty infiltration of the myocardium found at autopsy. Note the large amplitude of *Q-R-S*<sub>4</sub> which is the only abnormality in this lead. There is slurring in the standard 3 leads, a negative *S-T*<sub>1</sub> and a positive *S-T*<sub>3</sub>, left axis shift and a late ventricular extrasystole in Lead II. In this and subsequent figures the 4 leads are indicated by Roman numerals.

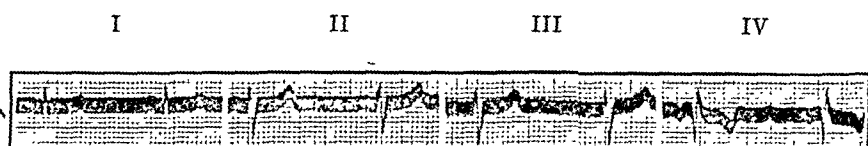


FIG. 2.—Moderate coronary sclerosis, moderate myocardial fibrosis, fatty infiltration of the right ventricle and brown atrophy of the heart found at autopsy. Note the small amplitude of *Q-R-S*<sub>4</sub> which is the only abnormality in this lead. There is a decided left axis shift in the standard 3 leads.

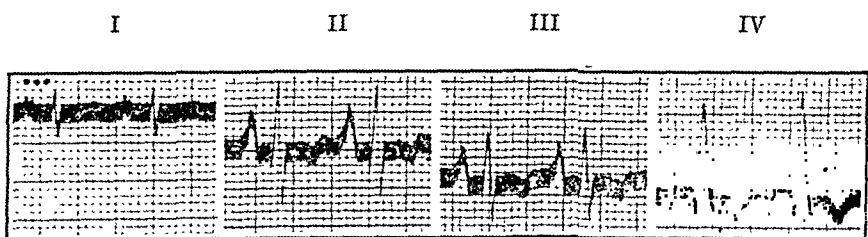


FIG. 3.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. Note the positive *Q-R-S*<sub>4</sub> type which is the only abnormality in this lead. There is a peculiar diphasic *Q-R-S* in the standard leads, negative *T*<sub>2</sub> and *T*<sub>3</sub> and large *P*<sub>2</sub> and *P*<sub>3</sub>.

*S-T* segment was usually within normal limits (Figs. 6, 14, 15 *C*, *D*, 16), but in 4 instances it was positive (Fig. 15 *B*). The *T* wave was within normal limits in 10 instances (Figs. 6, 14 *A*, 15 *E*) and positive or diphasic in the remaining 6 (Figs. 15, 16). There were 5 instances of intraventricular block in this group (Figs. 15, 16).

Neither one of the two  $Q-R-S_4$  types was constantly associated with either one of the  $Q$  types described in the standard 3 leads by Wilson *et al.*<sup>2</sup>

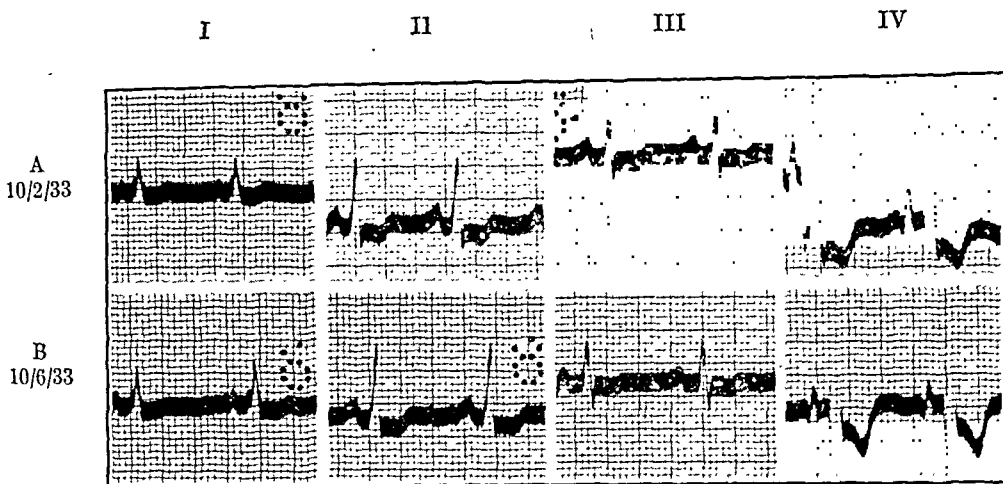


FIG. 4.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. The 2 records were taken just before the patient's death. Note the positive  $Q-R-S_4$  type, the markedly depressed  $S-T_4$  and the positive  $P_4$ , which are all abnormal. The  $Q-R-S$  is slurred in the standard 3 leads,  $S-T_1, 2$  and  $3$  is depressed and  $T_1, 2$  and  $3$  is not discernible.

In the *positive and diphasic  $T_4$  type*, which occurred 50 times in 200 cases, the  $T$  wave was positive in 13 (Figs. 5, 9 *E*) diphasic with the 1st phase negative in 30 instances (Figs. 7, 8, 9, 10 *A*) and diphasic with the 1st phase positive in 7 (Figs. 13 *C*, 15 *B*, 16 *B*). The  $Q-R-S$  complex was usually diphasic and not abnormal (Fig. 13 *C*), although there were 16 instances with a positive  $Q-R-S_4$

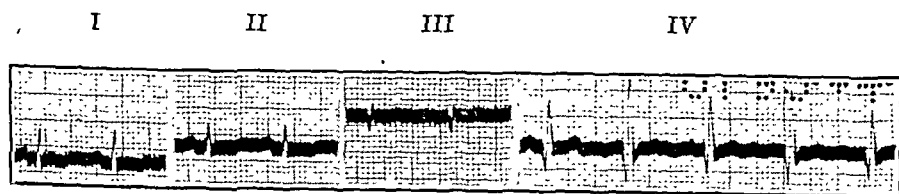


FIG. 5.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. Note the positive  $Q-R-S_4$  and positive  $T_4$  types with W-shaped  $Q-R-S$  complex and electrical alternans. There is low "voltage" in the standard 3 leads, left axis shift, slightly depressed  $S-T_1$  and  $2$  and negative  $T_1$ .

type (Figs. 5, 7, 8, 9, 10 *A*) and 4 with a negative  $Q-R-S_4$  type (Figs. 15 *B*, 16). The  $S-T$  segment was usually within normal limits (Figs. 10 *A*, 16). It was deeply negative 8 times (Figs. 7, 8 9) and positive 8 times (Figs. 13 *C*, 15 *B*). There were 6 instances of intraventricular block in this group (Figs. 13 *C*, 15, 16). This group was associated with a negative  $T_1$  or the  $T_1$  type of Parkinson and Bedford<sup>12</sup> only 5 times.



In the *deeply negative  $T_4$  type*, which occurred 14 times in 200 cases, the  $T$  wave was 8 mm. or more in depth (Fig. 11). In all but 3 instances this was associated with the positive  $Q-R-S_4$  type (Fig. 11). In the exceptions the  $Q-R-S$  complex was diphasic and normal. The  $S-T$  segment was always negative, but in only 8 instances was it outside normal limits. There were 4 instances of intraventricular block, all with a positive  $Q-R-S_4$  type. This group was occasionally (5 instances) associated with a negative  $T_3$  or the  $T_3$  type, (Parkinson and Bedford<sup>12</sup>).

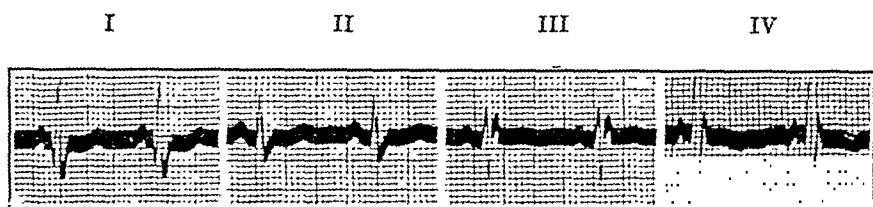


FIG. 6.—Moderate coronary sclerosis, myocardial fibrosis and syphilitic aortitis found at autopsy. Note the negative  $Q-R-S_4$  type with M-shaped  $Q-R-S$  complex. There is intraventricular block of the indeterminate type, with  $Q-R-S_1$ , 2 and 3 slurred and  $Q-R-S_3$  inverted.  $S-T_1$  is depressed and  $S-T_3$  elevated.

Several other abnormalities were observed. The diphasic  $Q-R-S_4$  was sometimes unusually large (Fig. 1) or unusually small (Fig. 2) or was the mirror image of normal in that the 1st phase was positive and was followed by a negative phase of equal magnitude (Fig. 16 C).

5. *The Appearance of Lead IV in the Presence of Certain Abnormalities of the Standard 3 Leads in the 100 Patients With Coronary Sclerosis (Group I, Series A).* Of the 100 patients with coronary

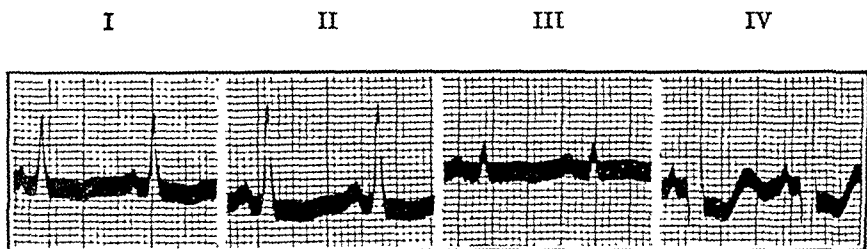


FIG. 7.—Moderate coronary sclerosis and moderate myocardial fibrosis found at autopsy. Note the positive  $Q-R-S_4$  and diphasic  $T_4$  types, the markedly depressed  $S-T_4$  and positive  $P_4$ . There is slurring of  $Q-R-S_1$ , 2 and 3, depression of  $S-T_1$  and 2, small  $T_1$ , 2 and 3 and inversion of  $T_1$  and 2.

sclerosis in Series A, 75 showed a left axis shift or a left ventricular preponderance, but this did not noticeably influence the direction of the major  $Q-R-S$  deflection in Lead IV. It is interesting that 33 of the 39 instances of the positive  $Q-R-S_4$  type without intraventricular block were in this group and only 1 of the 6 instances of the negative  $Q-R-S_4$  type without intraventricular block was in this group. This agrees with the observations of Masters,<sup>9</sup> who

found that left axis shift had little influence on the direction of  $Q-R-S_4$  complex.

Low "voltage" of  $Q-R-S$  in the standard 3 leads which occurred 10 times in this series was never associated with low amplitude in Lead IV.

There were 14 instances of the  $T_1$  type of Parkinson and Bedford and 35 instances of the  $T_3$  type in this series. These were associated with the various types of Lead IV as well as with a normal Lead IV.

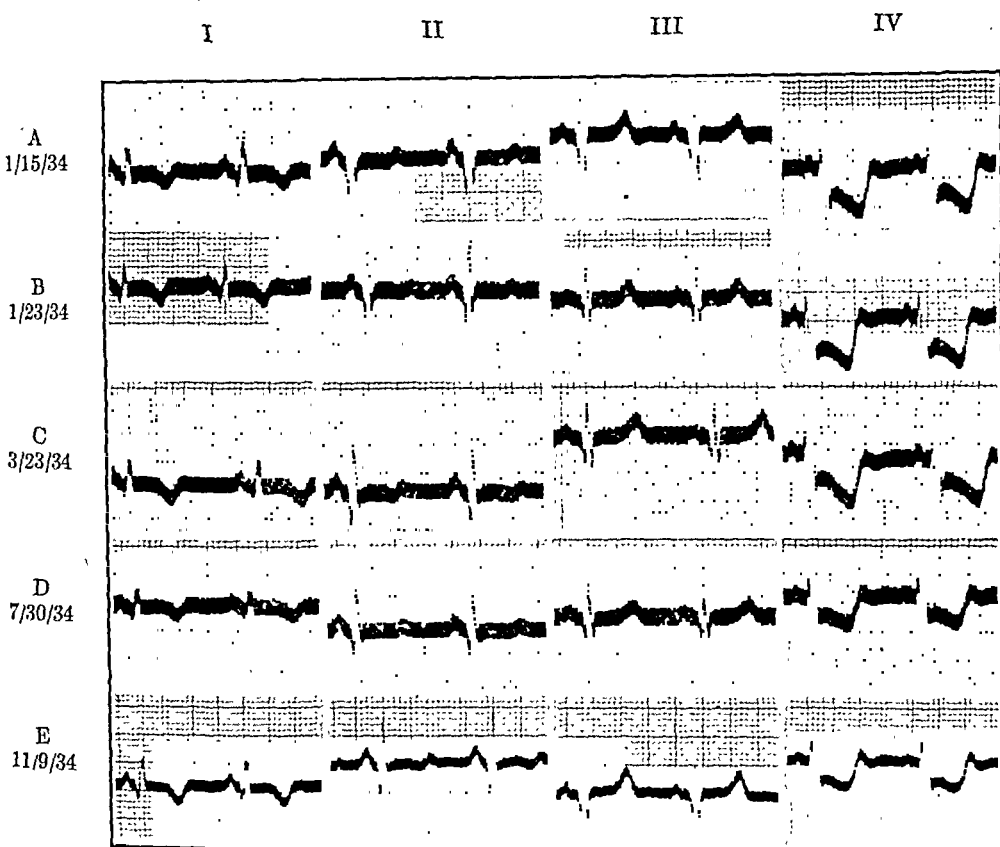


FIG. 8.—Chronic non-progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the practically constant appearance of the 4 leads over a period of 10 months. Note also the positive  $Q-R-S_4$  and diphasic  $T_4$  types, the markedly depressed  $S-T_4$  and the positive  $P_4$ .  $Q-R-S_{1, 2}$  and 3 is slurred. There is a  $Q_1$  and in later records a  $Q_2$ ,  $S-T_3$  is elevated slightly.

The same was true of the 27 instances of the  $Q_1$  of Wilson and the 35 instances of the  $Q_2$  type in this series.

Masters<sup>9</sup> has suggested that Lead IV might be of service in differentiating  $T_3$  inversions, which are a normal variant from those which are indicative of abnormality. In Series A of our cases of coronary sclerosis, there were 34 instances of negative  $T_3$ , 24 of which had an abnormal Lead IV.

There were 9 patients with intraventricular block of the common

bundle-branch type or indeterminate type in Series A. Five of these had a negative  $Q-R-S_4$  type, some being of the common bundle-branch type, others of the indeterminate. In the latter, the  $Q-R-S_4$  resembled a W and was small (Fig. 15 B). Three of the others which were of the common type of bundle-branch block showed the positive  $Q-R-S_4$  type. The 9th, of the indeterminate type, had a diphasic  $Q-R-S_4$  complex. Hoffman and Delong<sup>13</sup> reported that in their 6 cases of bundle-branch block the  $Q-R-S_4$

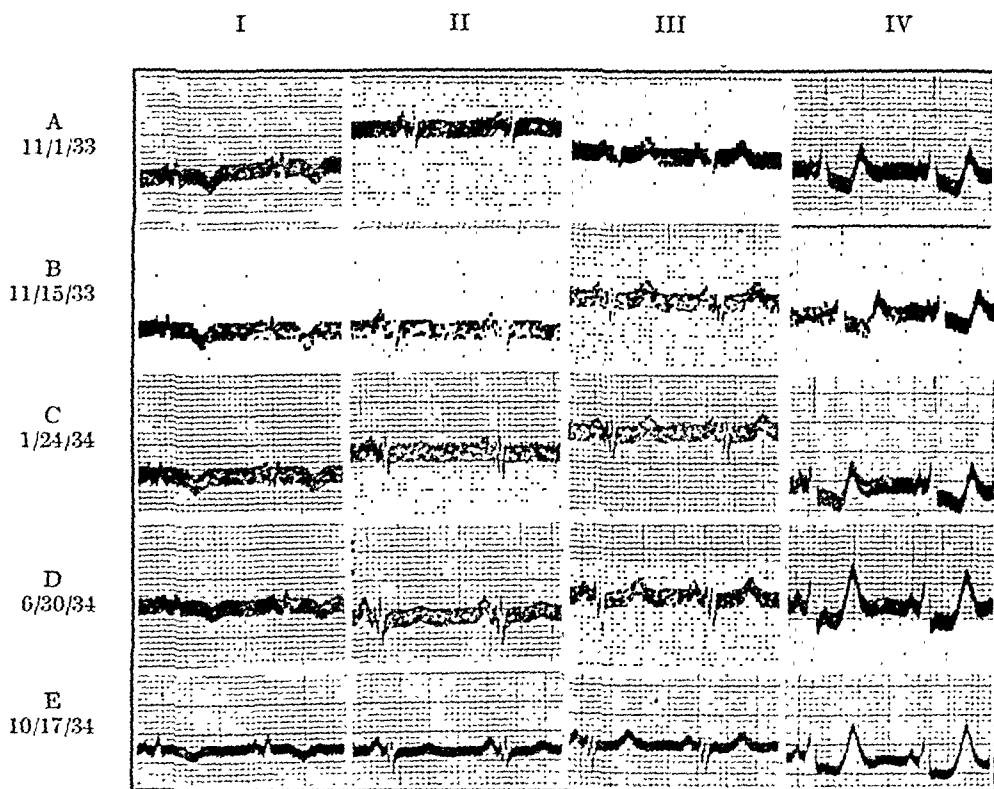


FIG. 9.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the slow progression of the T wave in Lead IV over a period of a year. Note the positive  $Q-R-S_4$  and diphasic and positive  $T_4$  types, the markedly depressed  $S-T_4$  and eventually positive  $P_4$ .  $Q-R-S_1$ , 2 and 3 are small, slurred and there is a left axis shift;  $T_1$  is inverted.

was normal except for widening of the  $Q-R-S$ . It is difficult to say what significance the various types of  $Q-R-S_4$  encountered in intraventricular block may have; but in view of the recent studies by Wilson *et al.* with precordial leads<sup>14</sup> and the observation made on the  $Q-E$  interval by Nichol,<sup>15</sup> Wolferth *et al.*<sup>16</sup> and Katz, Landt and Bohning,<sup>17</sup> it is possible that the 4th lead may be found to be of value in helping to determine the location of the intraventricular block. This we are now investigating further.

6. *The 4-lead Electrocardiogram in Patients With Coronary Sclerosis Confirmed at Postmortem.* There is very little information in the literature concerning the 4-lead electrocardiogram in instances of coronary sclerosis confirmed at autopsy. We are, therefore, reporting our findings in 7 such instances, the clinical diagnosis of coronary sclerosis having been confirmed postmortem by Dr. O. Saphir, of the Department of Pathology. The sclerosis was found

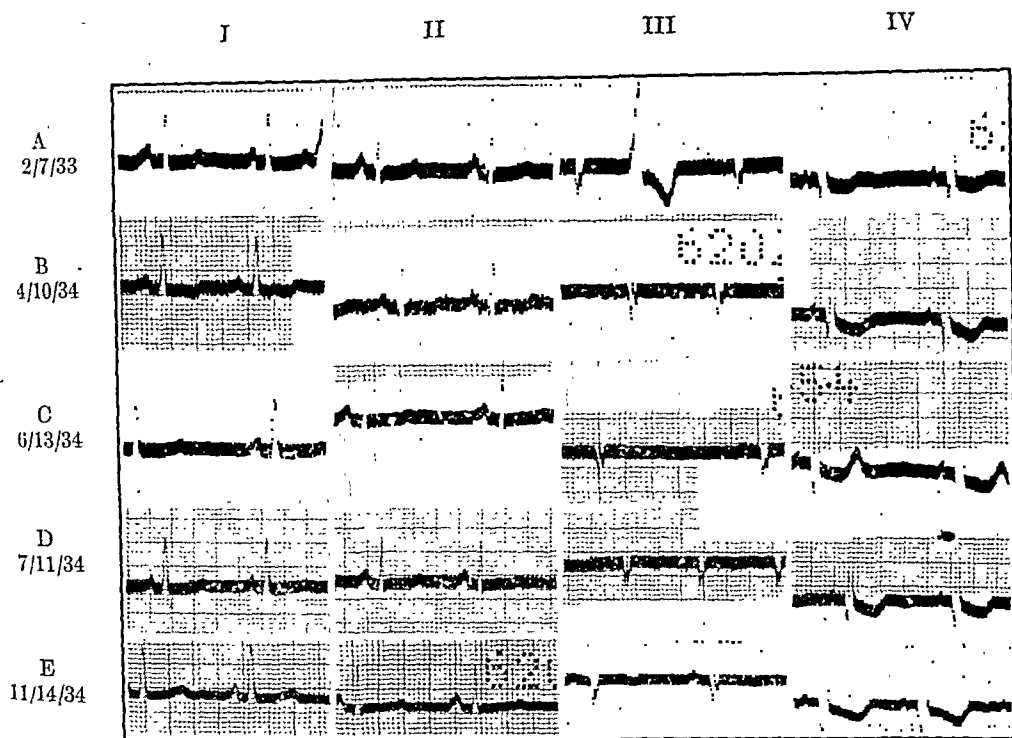


FIG. 10.—Chronic non-progressive coronary insufficiency on which is superimposed a subacute coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis who had an attack of clinically diagnosed recent coronary occlusion in June, 1934. Note the practically constant appearance of Lead IV over a period of 1 year and 5 months except for the temporary change in segment C when the patient had coronary occlusion. The change consisted in the appearance of a positive  $T_4$  type with some depression of  $S-T_4$ , the standard 3 leads showing no change. The record shows a positive  $Q-R-S_4$  type and in Segment A, a diphasic  $T_4$  type. There is a noticeable sinus arrhythmia. In Lead III of Segment A there is a ventricular extrasystole. There is left axis shift.  $S-T_1$  and 2 is depressed and  $T_1$ , 2 and 3 is small.

to be moderate to advanced in all 7 and was associated with moderate or extensive myocardial fibrosis. The important detailed findings are given in the legends of Figs. 1 to 7.

In none of the 7 was Lead IV normal. In one the abnormality consisted of a tremendously large diphasic  $Q-R-S_4$  (43 mm.) associated with a negative  $S-T_1$ , slurred  $Q-R-S_{1,2,3}$  and left axis shift (Fig. 1). In a 2d the abnormality consisted of a small  $Q-R-S_4$

associated with a left ventricular preponderance (Fig. 2).<sup>\*</sup> In a 3d instance the abnormality consisted of a positive  $Q-R-S_4$  type accompanied by several abnormalities in the standard 3 leads, especially large  $P_2$  and  $_3$  (Fig. 3). In a 4th the abnormality in Lead IV consisted of a marked depression of the  $S-T$  segment associated with similar  $S-T$  depressions in the other 3 leads; a positive  $Q-R-S_4$  type and a positive  $P_4$  were also present (Fig. 4). The changes between records in this case are probably due to the moribund condition of the patient. In a 5th the  $Q-R-S_4$  was mainly up and triphasic (W), and was associated with the positive  $T_4$  type (Fig. 5). Low "voltage," a left axis shift,  $S-T$  depressions in Leads I and II were also present. Another interesting feature is found in an electrical alternans in Lead IV. In the 6th the abnor-

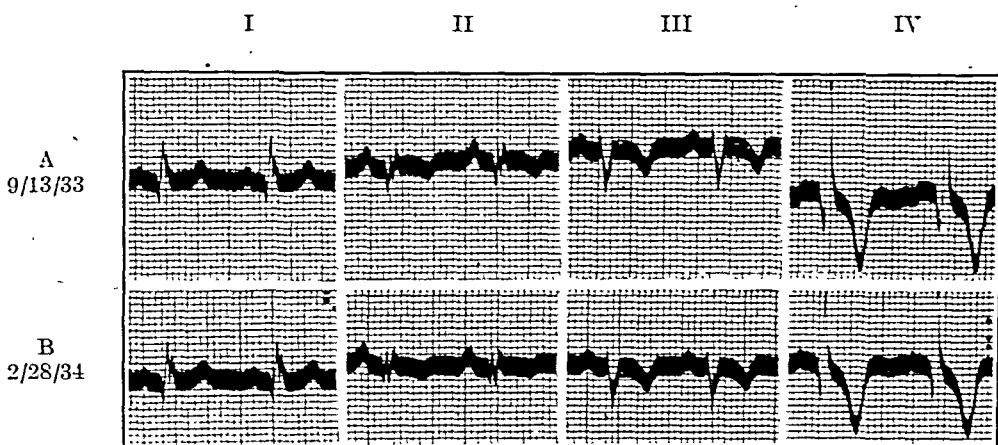


FIG. 11.—Chronic non-progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the practically constant appearance of the 4-lead electrocardiogram over a period of 5½ months. Note the positive  $Q-R-S_4$  and the deeply negative  $T_4$  types. The  $Q-R-S$  complex is notched and small in Leads I, II and III, a  $Q_1$  is present and there is left axis shift;  $T_1$  and  $_2$  is inverted.

malities consisted of an indeterminate intraventricular block with a negative  $Q-R-S_4$  type, the complex being triphasic and M shaped (Fig. 6). In the 7th, the abnormality consisted of a markedly depressed  $S-T_4$ , a diphasic  $T_4$  (1st phase negative) and  $Q-R-S_4$  mainly up (Fig. 7). The standard 3 leads were also abnormal.

This small series of autopsied cases, we believe, confirms the interpretation that Lead IV is of value in helping determining the status of the coronary circulation.

7. *The Value of Serial 4-lead Electrocardiograms in Coronary Disease.* Early during the course of this study we were impressed with the resemblance of some of Lead IV's obtained in patients with

<sup>\*</sup> This was a very interesting finding since brown atrophy was present. This has been dealt with elsewhere by Katz, Saphir and Strauss.<sup>15</sup>

coronary sclerosis to those seen following a coronary occlusion, but unlike the latter, these aberrations persisted practically unchanged for months or changed slowly. This was especially true of the group of records showing the positive or diphasic  $T_4$  type (Figs. 8, 9). Patients with a recent coronary occlusion and myocardial infarction show abnormalities which progress and then regress rather rapidly in one or more of the leads of the 4-lead electrocardiograms and usually in Lead IV. For example, a negative  $T_4$  following the occlusion, becomes diphasic, then positive and later, over a

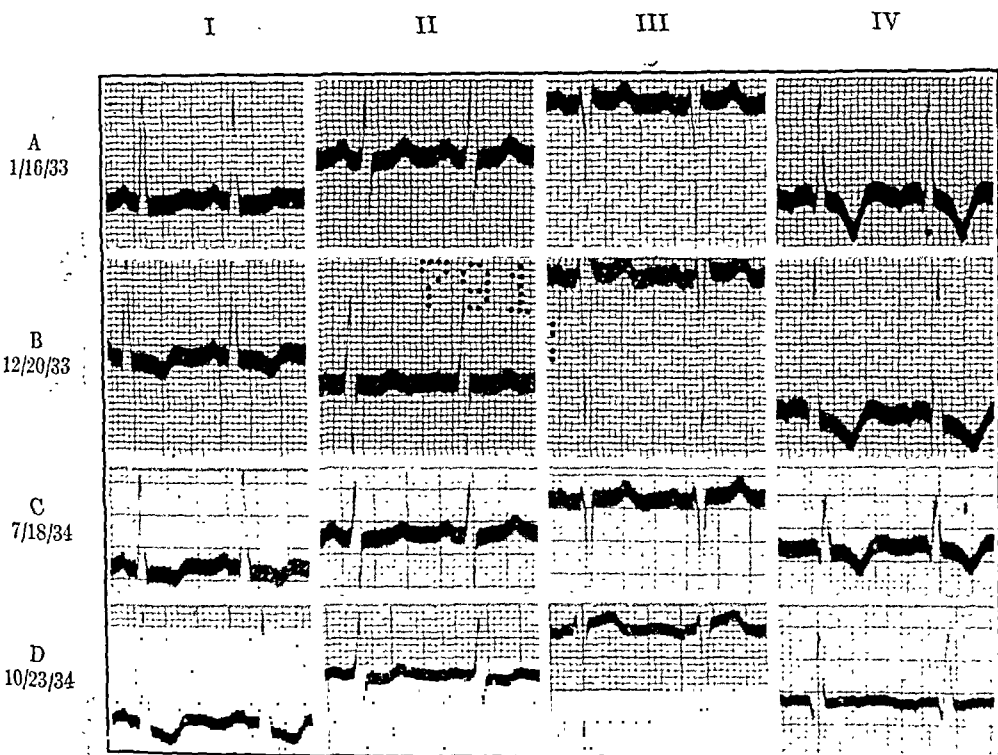


FIG. 12.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the slowly progressive decrease in  $Q-R-S_4$  and the decrease in size of  $T_4$  associated with progressive depression of  $S-T_1$  and  $_2$  and elevation of  $S-T_3$  over a period of 1 year and 9 months. Note the positive  $Q-R-S_4$  type associated with left ventricular preponderance, depressed  $S-T_1$  and  $_2$ , elevated  $S-T_3$  and negative  $T_1$ .

period of weeks, reverts back to a normal negative  $T$  wave (Katz and Bohning<sup>8</sup>). For example, in Fig. 10 is shown a patient with coronary sclerosis with a diphasic or negative  $T_4$  (Segments A and B) which became peaked and positive (Segment C) following an occlusion with myocardial infarction, and then in a few weeks reverted to its earlier form (Segment D). In striking contrast, the patients with coronary sclerosis maintained the diphasic or positive  $T$  wave in Lead IV for many months or over 1 year or more either unchanged or only slowly progressive (Figs. 8, 9).

These observations led us to study the changes in serial electrocardiograms systematically. A collection of serial electrocardiograms covering a period from 4 months to 2 years or more were obtained in 56 of the 200 patients with coronary sclerosis. An analysis of these records and, in addition, those obtained on patients with recent coronary occlusion and records obtained during this period in other conditions have led us to the following conclusion:

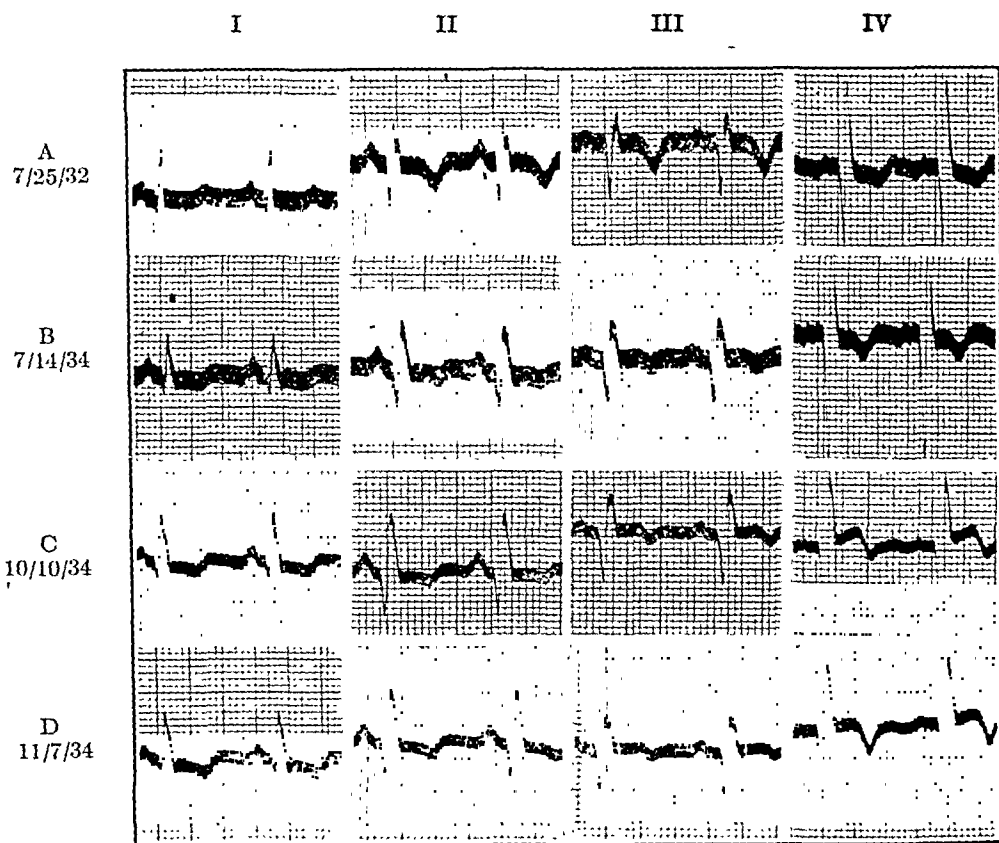


FIG. 13.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the progressive increase in Q-R-S duration, the S-T<sub>1</sub> elevation, the change from a biphasic T<sub>1</sub> with 1st phase negative to a biphasic T<sub>1</sub> with 1st phase positive over a period of 2 years and 3 months. This is associated with an inversion of T<sub>1</sub>, decreased inversion of T in Leads II and III and depression of S-T<sub>1</sub> and 2, elevation of S-T<sub>3</sub>. There is an indeterminate type of intraventricular block and Q<sub>2</sub> and Q<sub>3</sub> is present.

If one excludes records obtained from acute infectious cases, from moribund patients, and if one can exclude the effect of large doses of digitalis (Strauss and Katz<sup>19</sup>), then from the changes in serial 4-lead electrocardiograms it can be determined whether the coronary insufficiency is: (1) An acute coronary insufficiency, *i. e.*, angina pectoris, nocturnal dyspnea, cardiac asthma, or its equivalent; (2) a sub-acute coronary insufficiency, *i. e.*, recent occlusion, thrombotic or

arteriosclerotic with myocardial infarction; (3) a chronic non-progressive coronary insufficiency; or (4) a chronic progressive coronary insufficiency.

In acute coronary insufficiency which is usually superimposed on a chronic milder coronary insufficiency the changes in the 4-lead electrocardiogram are transitory and usually slight, such as occur following exercise in patients with chronic coronary insufficiency (Katz and Landt<sup>20</sup>). These changes are transitory, lasting only for a few minutes or hours after which the 4-lead electrocardiogram returns to its preëxisting contour. We have seen 7 instances where this has occurred spontaneously. In some, these changes were accompanied by attacks of angina pectoris. In others, no angina pectoris accompanied the condition but, instead, only vague symp-

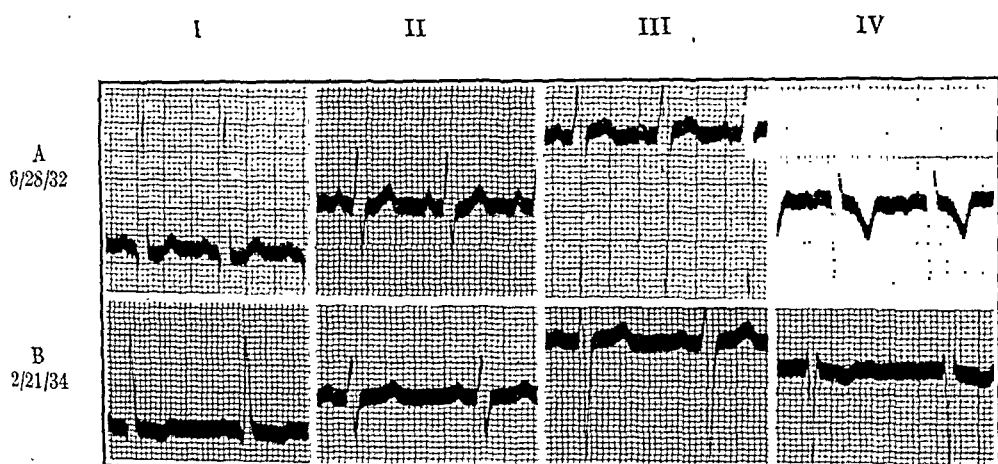


FIG. 14.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the decrease in  $T$  over a period of 1 year and 8 months, associated with inversion of  $T_1$ . Note the negative  $Q-R-S_1$  type which in Segment B is M shaped. There is left ventricular preponderance and depressed  $S-T_1$  and elevated  $S-T_3$ .

toms occurred. It is possible that similar changes will occur when the patient has an attack of paroxysmal cardiac dyspnea. We believe that such changes in the electrocardiogram are brought about by any condition in which the coronary blood supply becomes inadequate for the work the heart is doing, either because the former declines suddenly or the latter increases abruptly. Factors which bring about such a disbalance have been discussed elsewhere (Katz<sup>21</sup>).

In the subacute coronary insufficiency, the inadequacy of the coronary circulation persists long enough to cause myocardial infarction. This may be due to thrombotic closure, to arteriosclerotic closure, or to arteriosclerotic narrowing and congestive heart failure (Saphir, Priest, Hamburger and Katz<sup>3</sup>). Here the changes in the electrocardiogram are more marked and progress over a period of days, weeks or a month or more if the patient survives,



before returning toward normal. This is the period of time required to establish an adequate collateral circulation. This group is discussed in detail elsewhere (Katz and Bohning<sup>6</sup>).

In the chronic non-progressive coronary insufficiency, the 4-lead electrocardiogram shows abnormalities which are practically stationary over long periods of time, months or years. We have 36 instances of this group (Figs. 8, 10 A, D, 11). In this group it would seem that the collateral circulation keeps pace with the inadequacies

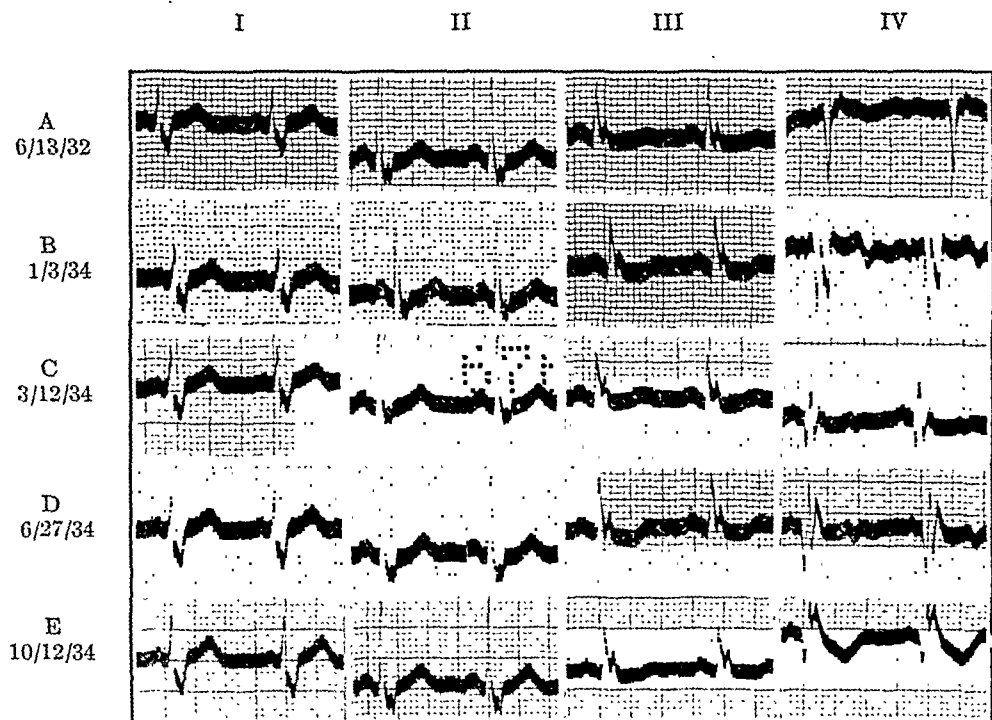


FIG. 15.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note the progressive change in contour of Lead IV over a period of 2 years and 4 months. Note that the negative  $Q-R-S_4$  type changes to a diphasic type, that in Segment B the  $Q-R-S_4$  has a W form, that the positive  $S-T_4$  becomes negative, that the diphasic  $T_4$  becomes negative, that  $P_4$  becomes positive and that the  $S-T$  becomes positive in Lead I and negative in Lead III. There is an intraventricular block of the indeterminate type.

of the circulation either because, on the one hand, the pathologic changes are developing slowly or not at all, or, on the other hand, because the impairment is not too far advanced so that the collateral circulation can keep pace with the pathologic process. In any event the outlook in such patients, other things being equal, should be better barring the intervention of a thrombus, than in the succeeding group.

In the chronic progressive coronary insufficiency, the 4-lead electrocardiograms show abnormalities which progress slowly over

a period of months, or a year or more. We have 20 instances of this group in this series (Figs. 9, 12, 13, 14, 15, 16 and 17). In this group the collateral circulation cannot keep pace with the pathological process either because the anatomic changes are far advanced or because cardiac congestive failure is occurring.

It must be borne in mind that, while the last group includes for the most part the more abnormal electrocardiograms, nevertheless, there is no correlation between the degree of electrocardiographic abnormality and the rate of progression of the abnormalities (*cf.* Figs. 8, 17). Serial electrocardiograms, we believe, should be taken in all

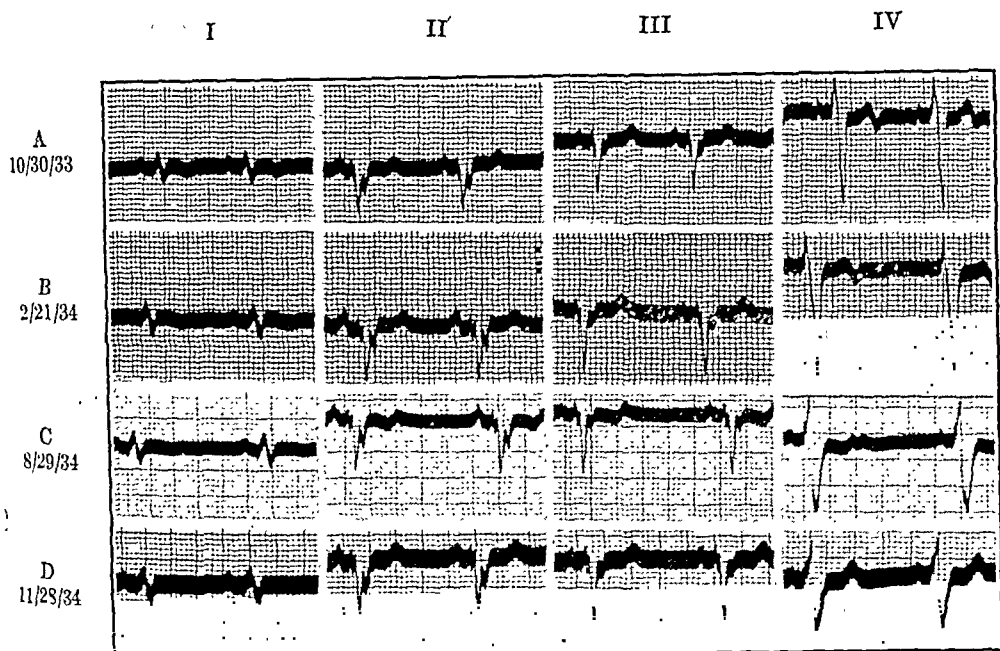


FIG. 16.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis. Note that the S-T segment in Lead IV becomes depressed and the diphasic  $T_4$  becomes positive over a period of 13 months, at the same time that  $T_2$  and  $T_3$  become diphasic and  $P_4$  positive. There is an intraventricular block of the common bundle-branch type. Note that in Segments A and B there is a negative Q-R-S<sub>4</sub> type and in Segment C, a diphasic Q-R-S; in all, however, the 1st phase is positive.

patients suspected of chronic coronary insufficiency and an estimate made of the degree of the inadequacy of the circulation and the rate of progression from the records so obtained. This estimate, we believe, is of decided assistance to the clinician when correlated with his judgment based on his clinical findings. We believe that this electrocardiographic evaluation is particularly useful because of the paucity of the clinical evidence in a large group of such patients. Indeed, further studies along these lines may offer a useful aid in prognostic studies as, for example, life insurance evaluations. We have pointed out elsewhere the added value of a graded exercise test for this purpose (Katz and Landt<sup>20</sup>).

Finally, it may be emphasized that the 4th lead is a definite aid, not because the abnormalities are confined to this lead alone, but because the changes are so often more noticeable in this lead than in the others. Furthermore, the deviation from normal in this lead often bears a reciprocal relationship to the deviation from normal in the standard 3 leads.

The changes in the 4-lead electrocardiogram seen in coronary disease are expressions of damages to the myocardium brought on by inadequacies of the coronary circulation. The *S-T* deviations are due to injury currents set up in various parts of the muscle mass as a result of injury to the myocardium. These currents actually disappear once the injured tissue is dead (Korey and Katz<sup>22</sup>). The *T*-wave changes are brought about by a long delay in the arrival of the impulse to the injured areas (Katz<sup>23</sup>). Conduction is the

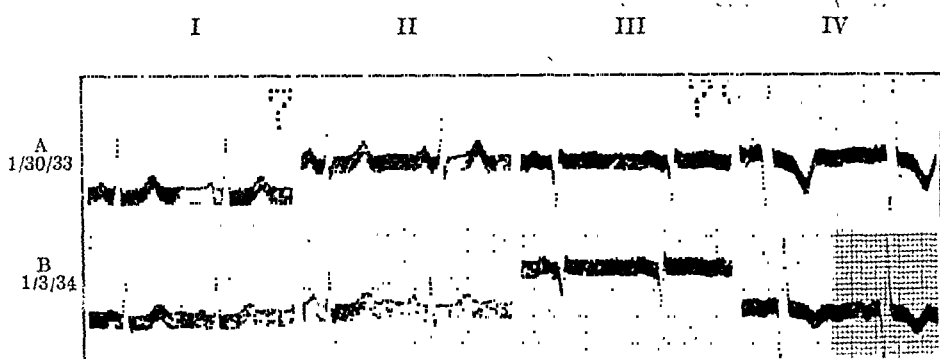


FIG. 17.—Chronic progressive coronary insufficiency shown in series of 4-lead electrocardiograms from patient clinically diagnosed coronary sclerosis: Note that while both records of Lead IV are normal there is a change between them, *viz.*, *T*<sub>4</sub> is smaller in Segment B and *S-T*<sub>4</sub> formerly depressed is now isoelectric. This change occurred over a period of 11 months and is associated with *S-T*<sub>1</sub> and <sub>2</sub> depression and decrease in *T*<sub>1</sub> and <sub>2</sub>. There is left axis shift in *Q*<sub>3</sub> and slurring of *Q-R-S*<sub>1</sub>, <sub>2</sub> and <sub>3</sub>.

most labile physiologic property of the heart and the first to be affected and the last to return to normal when cardiac muscle is damaged or malnourished.\* These facts offer a rational explanation of the correlation we have established between the electrocardiographic changes and the degree and course of the coronary insufficiency. This functional classification should prove as useful in evaluating the clinical course of the patients as the anatomic and etiologic classifications.

**Summary.** 1. A total of 508 electrocardiograms taken with a Lead IV have been analyzed and the data tabulated and summarized. Two hundred were from patients clinically diagnosed to have coronary sclerosis, 50 from patients suspected of having coronary sclerosis but without definite symptoms, 100 from patients with

\* The *Q-R-S* abnormalities have been explained by Wilson *et al.*<sup>2</sup> as the result of the absence of the electrical effects of the destroyed areas.

suspected cardiac disease, 25 from individuals with normal hearts and 133 from patients known to have other types of organic heart disease.

2. It was found that patients with coronary sclerosis showed abnormalities in Lead IV more often than any of the control groups.

3. The abnormalities in Lead IV in the patients with coronary sclerosis were almost always associated with abnormal findings in the conventional 3 leads, but the deviations were usually more striking in Lead IV.

4. Patients with coronary sclerosis having clinical evidence of myocardial incompetence showed abnormalities in Lead IV more often than patients without such myocardial incompetence.

5. The 4 major types of abnormal Lead IV found in patients with coronary sclerosis are described. They are the positive  $Q-R-S_4$  type (the most common), the negative  $Q-R-S_4$  type, the positive and diphasic  $T_4$  type and the deeply negative  $T_4$  type.

6. The value of Lead IV in determining the status of the coronary circulation was confirmed by postmortem examination in 7 cases of coronary sclerosis.

7. Serial 4-lead electrocardiograms were obtained in 56 of the 200 patients with coronary sclerosis covering a period of from 4 months to 2 years or more. Analysis of these records and, in addition, those obtained on patients with recent coronary occlusion and other conditions showed the value of serial electrocardiograms in evaluating the state of the coronary circulation. This is particularly important because of the paucity of precise clinical evidence in a large number of such patients.

8. If records obtained in patients suffering from acute infectious processes, those taken on moribund patients, and those due to large doses of digitalis are excluded, then one can determine from serial 4-lead electrocardiograms whether the coronary insufficiency is: (1) An acute transitory coronary insufficiency, *i. e.*, angina pectoris, nocturnal dyspnea, cardiac asthma, or its equivalent; (2) a subacute coronary insufficiency, *i. e.*, recent occlusion, thrombotic or arteriosclerotic, with myocardial infarction; (3) a chronic non-progressive coronary insufficiency; or (4) a chronic progressive coronary insufficiency. This functional classification should prove as useful in evaluating the clinical course of the patients as the anatomic and etiologic classifications.

9. This study emphasizes the importance of taking serial 4-lead electrocardiograms in all patients suspected of having coronary disease in estimating the degree of insufficiency of the coronary circulation and the rate of its progress.

We are indebted to Dr. P. Markle for technical assistance, and to the Medical Staff of the Hospital for permission to use the records of their private patients in this study.

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## CORONARY THROMBOSIS AND ITS EFFECT ON THE SIZE OF THE HEART.

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ALTHOUGH it has been recognized for many years that arteriosclerosis of the peripheral vessels does not *per se* cause cardiac enlargement, statements are made that coronary artery disease results in an increased weight of the heart.<sup>1,2,3,4</sup> Others believe that some extra coronary mechanism is responsible for cardiac hypertrophy found in persons with coronary disease.<sup>5,6,7</sup> Prolonged exercise, following experimental cardiac infarction in dogs, does not result in cardiac hypertrophy.<sup>8</sup>

There has not been published a follow-up study of patients with coronary occlusion who had a normal sized heart at the time of the

occlusion to determine whether cardiac hypertrophy ensued. This report is such a study. A total of 20 cases was followed. All had definite clinical and electrocardiographic evidence of an acute coronary obstruction. Fluoroscopic or orthodiagraphic examination revealed in every case a normal sized heart. The examinations were made by one or both of us. All the patients were males. The ages were from 30 to 76 years. The average time from the first to the last Roentgen examination was  $3\frac{5}{6}$  years. The shortest was 5 months, the longest 9 years and 10 months. In many of the cases repeated interim Roentgen ray examinations were made. In no instance was there found any increase in the size of the heart. Aneurysm and acute dilatation of the heart which occasionally follow coronary thrombosis and which might simulate cardiac hypertrophy were not encountered. Three of the patients are dead. Autopsy in 1 case 5 months after the coronary accident confirmed the clinical diagnosis. Table 1 is a summary of the data.

TABLE 1.—ANALYSIS OF 20 CASES SHOWING NORMAL HEART SIZE AFTER CORONARY OCCLUSION.\*

Case No.	Age.	Initial Roentgen ray.		Size of heart.	Final Roentgen ray.		Size of heart.
		Date.			Date.		
1	51	Aug. 13, 1928		Normal	May 4, 1934		Normal
2	58	March 17, 1927		Normal	Feb. 16, 1934		Normal
3	30	June 1, 1925		Normal	June 8, 1934		Normal
4	58	Jan. 11, 1926		Normal	Feb. 18, 1930		Normal
5	50	Feb. 23, 1932		Normal	May 25, 1934		Normal
6	44	June 18, 1932		Normal	May 26, 1934		Normal
7	42	March 4, 1924		Normal	Jan. 8, 1934		Normal
8	48	Oct. 10, 1931		Normal	Dec. 30, 1932		Normal
9	66	Oct. 7, 1931		Normal	July 7, 1933		Normal
10	64	Feb. 24, 1932		Normal	July 7, 1932		Normal
11	45	Oct. 5, 1927		Normal	Feb. 8, 1932		Normal
12	41	Oct. 6, 1926		Normal	June 15, 1929		Normal
13	47	June 1, 1933		Normal	June 7, 1934		Normal
14	58	Sept. 6, 1928		Normal	Feb. 12, 1932		Normal
15	55	Aug. 1, 1931		Normal	May 14, 1934		Normal
16	61	July 23, 1928		Normal	Feb. 18, 1931		Normal
17	42	June 7, 1928		Normal	April 16, 1929		Normal
18	53	June 26, 1931		Normal	June 8, 1934		Normal
19	49	March 6, 1925		Normal	May 25, 1934		Normal
20	76	Nov. 1, 1932		Normal	May 28, 1934		Normal

\* All males.

**Comment.** In any discussion of the cause of cardiac hypertrophy in a patient without an elevated blood pressure a pre-existing hypertension which could cause the cardiac enlargement must be excluded. Such a possibility has not always been considered and probably accounts for the confusion in the literature as to the association of coronary disease and cardiac hypertrophy. Even though the former level of the blood pressure is unknown, clinical or pathological evidence of an antecedent hypertension should be sought for. Aside from the cardiac hypertrophy, which of itself may be proof

of a former hypertension, these patients may show impairment of renal function or uremia, a roentgenologic cardiac silhouette suggesting hypertension, coronary types of electrocardiograms as are so often found in known hypertensive individuals, ophthalmoscopic signs of a previous hypertensive state, arteriolar sclerosis of the voluntary muscles as observed in biopsy specimens, and finally autopsy may disclose arteriolar lesions which always evidence a persistent hypertension during the life of the individual.<sup>9</sup>

**Summary.** Twenty patients who had a normal sized heart at the time they experienced a coronary thrombosis did not develop roentgenologic evidence of cardiac enlargement although they were observed from 5 months to 9 $\frac{5}{8}$  years.

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## BOOK REVIEWS AND NOTICES

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**SURGICAL DISEASES OF THE CHEST.** By EVARTS AMBROSE GRAHAM, A.B., M.D., F.A.C.S., Professor of Surgery, Washington University School of Medicine, St. Louis; Surgeon-in-Chief, Barnes Hospital and St. Louis Children's Hospital, etc.; JACOB JESSE SINGER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician, Barnes Hospital, etc., and HARRY C. BALLON, M.D., C.M., F.A.C.S., Formerly Assistant Professor of Surgery, Washington University School of Medicine; Formerly Assistant Surgeon, Barnes Hospital. Pp. 1070; 637 illustrations. Philadelphia: Lea & Febiger, 1935. Price, \$15.00.

It is difficult to do adequate justice to this volume. Within 1070 pages the authors have thoroughly covered the surgical lesions of the chest. The subject matter is delightfully presented, adequately discussed and brings to the reader the wealth of the author's knowledge of the subject. The illustrations are well done and clearly bring out the points for which they are intended. Special chapters have been contributed by Ray W. Matson, Helen Lamb, David H. Ballon and Ralph C. Matson. There are 22 chapters beginning with a brief discussion of "Some Physiological Considerations of Importance to the Thoracic Surgeon" and ending with a presentation of the senior author's chest service at the Barnes Hospital.

The Table of Contents leaves nothing to be desired. This work is more than a thoracic surgery, for it covers the medical aspects of thoracic lesions which have a surgical significance just as carefully as it does the surgical technique. The lesions of the thoracic cage, pleura, lungs and bronchi, mediastinum, pericardium, heart, esophagus and diaphragm are adequately presented. Anesthesia, bronchography and bronchoscopy and pneumolysis are thoroughly reviewed.

Truly here is a work which every surgeon must have in his library and which most internists will do well to possess. Within its field it occupies a preëminent position.

I. R.

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**DIABETES MELLITUS AND OBESITY.** By GARFIELD G. DUNCAN, M.D., C.M. (McGILL), Associate in Medicine in the Jefferson Medical College, Philadelphia; Assistant Physician to the Pennsylvania Hospital, etc. With an introduction by THOMAS McCRAE, M.D., Professor of Medicine in the Jefferson Medical College, etc. Pp. 215; 9 illustrations and 40 tables. Philadelphia: Lea & Febiger, 1935. Price, \$2.75.

THE book contains chapters on the etiology, incidence and pathology of diabetes; on food and food metabolism which present the practical physiology; symptoms and diagnosis; diabetes in children; the prevention and treatment of diabetes, and on its complications. There is a chapter on the clinic and ward routine for diabetics and one on laboratory methods. The section on obesity comprises four short chapters. There is the usual appendix of food values and average weight tables.

It is apparent from this that the author is presenting the subject in textbook outline and for physicians. The material is of textbook caliber and the whole book is exceptionally well written with a directness and clarity that could hardly be improved. There is relatively little bibliography and no attempt is made to present the complex medical ideas in the field of



metabolism. The chapter on clinic and ward routines for the diabetic with and without various complications will be welcomed by the practitioner who wishes exact directions rather than principles. The section on obesity is simple, sufficiently resourceful and wisely avoids all fads. The book as a whole is a manual of diabetes and obesity for the physician, most of which is in language that he can use in the instruction of his patient, and should be of very real value to the practitioner. F. L.

**ATLAS FUNDUS OCULI.** By WILLIAM HOLLAND WILMER, M.D. (University of Virginia), LL.D. (Georgetown University), Sc.D. (Princeton and New York Universities), Professor of Ophthalmology and Director of the Department of Ophthalmology of the Johns Hopkins University School of Medicine; Ophthalmologist-in-Chief to the Johns Hopkins Hospital, etc. Introduction by WARFIELD T. LONGCOPE, M.D., Professor of Medicine and Director of the Department of Medicine of the Johns Hopkins School of Medicine, Pp. 100; 100 colored plates. New York: The Macmillan Company, 1934. Price, \$35.00.

MEDICAL atlases are among the more enduring forms of memorials, as Baillie, Hope, Carswell and Cruveilhier testify, to consider the field of pathology alone. What more fitting than that a leader in his specialty should cap the climax of his active career with such a splendid monument to his own and to American ophthalmological achievement! But, as we have been told on good authority, this particular atlas is even more important as ranking at the very top in the important field of study of the eye grounds. After 13 plates of normal human and animal fundi, various pathologic conditions are portrayed. Among the more conspicuous are anomalies (6), atrophies (4), choroido-retinitis (19), arteriosclerosis (8), changes in blood diseases (6), neoplasma (5).

As pointed out by Dr. Longcope in the introduction, the Atlas derives its value from several sources: "In the first place, it may be regarded as a series of personal records, selected by Dr. Wilmer with the discretion and wisdom that comes with great experience, to illustrate the appearance of the fundus under normal conditions and in a great variety of pathologic states; in the second place, it furnishes through the histories, so excellently epitomized, the information necessary for a useful correlation of the pathologic lesions in the fundus with the disease from which the patient suffered; and in the third place, it unfolds before our eyes one beautiful reproduction after another, each one of which depicts the changes in the fundus with a brilliancy and accuracy that cannot be surpassed." Many years in the making—as may be seen from the various dates on the plates—with an obviously close coöperation between a competent artist and a clinician of wide experience working with extensive material, these beautiful, accurate, colored reproductions should stand as the court of last resort for many years. Colored photography will indeed have to go far before it can surpass this magnificent achievement. E. K.

**THE DANGEROUS AGE IN MEN.** A Treatise on the Prostate Gland. By CHESTER T. STONE, M.D., Clinical Assistant Surgeon, Urological Division, Bellevue Hospital, New York City; Urologist, Bergen County Hospital, Oradell, N. J.; Consultant Urologist, Rome State School, Rome, N. Y. Pp. 105. New York: The Macmillan Company, 1935. Price, \$1.75.

THE copy of this book that we received for review is one of the fourth printing since last July, and this is not surprising with its provocative title,

and chapter headings such as "When is a Man Old?" "A Word to the Wives," and so on. Even in the opening chapter, the conservative physician's antagonism is aroused by such statements as: "Medical authors have variously estimated that from 35 to 90% of all adult males have trouble with the prostate gland," "It is, therefore, the most important of the sexual organs," "Since without sexual power there can be no real bodily and mental strength or capacity, this power must be kept in a state of efficiency by the regular and proper exercise of the sexual function," "No organ in the human body can properly function without the stimulating aid of the internal secretion from the sex glands." Later, referring to an active sex life interrupted by continence, "Unless this patient again establishes his sexual life, or goes to a urologist for proper massage and treatment, he is sure of a prostatitis." Even in a book written for the laity, are such categorical statements justified or even expedient? Good advice is given, to be sure, about moderate exercise, diet and sleep, psychic and physical harmony and the need for medical advice; but these, we believe, are more than balanced by the unguarded presentations of half knowledge that are capable of causing much damage.

E. K.

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THE CYCLOPEDIA OF MEDICINE. INDEX TO VOLUMES 1 TO 12. GEORGE MORRIS PIERSON, Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS I. LEDERER, B.S., M.D., A. GRAEME MITCHELL, M.D. Pp. 415. Philadelphia: F. A. Davis Company, 1934. Price, \$120.00 for the set.

ALTHOUGH the topics discussed in the twelve volumes of the *Cyclopedia of Medicine* are arranged alphabetically, the material is so voluminous, and its arrangement of a necessity at times arbitrary, that the usefulness of the *Cyclopedia* depends in no small measure upon an adequate index. This need is fully met in the volume which has just appeared. The setting in bold-faced type of all references to treatment is a distinct advantage.

R. K.

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FRENCH MEDICINE. Volume 15 of *Clio Medica*. By M. LAIGNEL-LAVASTINE, Professor in the Medical Faculty in Paris; Secretary-General of the International Society of Medical History, and M. RAYMOND MOLINERY, Gold Medalist of the Academy of Medicine; Member of the French Society of Medical History. Translated by E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania. Pp. 187; 14 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, \$2.50.

To the *Clio Medica* series has been contributed a delightful little book on the history of medicine in France. Included subjects, described in interesting manner, are the curative magic of remote times, the primitive surgery of the Romans, the ecclesiastic origin of medical teaching and the strange plagues of the middle ages. The reader learns that the waters of the famous French Spas were recognized for their medicinal value in the earliest Gallo-Roman period, when great thermal stations were established. An account is given of the long succession of inspired pioneers in medicine—Lanfranc, Albertus Magnus, Bichat, Fernel, Paré, Laennec, Pasteur and many others whose work culminated in making Paris the center of the medical world of the 19th century. The book is very complete and suffers only from the brevity of description necessitated by so broad a subject.

L. L.

**DIE WERKE DES HIPPOKRATES.** Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würzburg. Regimen: Books 1 and 2 (Part 3, Price, Rm. 2.50); Books 3 and 4 (or Dreams), Regimen of Health (Part 4, Price, Rm. 2.10). Pp. Part 3, 98; Part 4, 80. Stuttgart: Hippokrates-Verlag G. M. B. H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

In the sense that in these 5 books the author offers a complex survey of the nature of man, they might be regarded as forming the very center of Hippocratic doctrine. Everything human is governed by natural law; health must be obtained by obeying these laws; disease results from a marked departure from them. The Regimen represents Hippocrates' "discovery" of how to regulate food and health so that health may be obtained; or disease, if present, be combated. This is indeed a great step beyond demonic pathology and magic treatment. The Regimen has a strong philosophic trend: far from holding close to observation, it makes free use of the imagination with a carefree disregard of truth of detail, so long as a truthful impression of the whole is conveyed.

These books are also characteristic of much of the Corpus, in that they are not definitely from the hand of Hippocrates himself—they are not even mentioned by Erotian, for instance. They have been divided by different scribes in different ways, an occurrence which accounts for the book on Dreams appearing as Book 4 of the Regimen; sometimes it was included without any separate title at all. Littré has one series of chapters for all four books. The weaknesses arising from detailing factual statements from a basis of unproved hypothesis are only too often apparent. Book 4 offers a detailed—and, of course, fanciful—explanation of the significance of dreams and the influence of heaven, of the earth and of the dead in their production.

In this edition, the interesting forewords and lists of contents that accompany each section are all the more valuable, as no index is as yet available.

E. K.

**PRACTICAL NEUROLOGICAL DIAGNOSIS.** With Special Reference to the Problems of Neurosurgery. By R. GLEN SPURLING, M.D., Assistant Clinical Professor of Surgery, in charge of neurosurgery, University of Louisville School of Medicine. Pp. 233; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, \$4.00.

STUDENTS and practitioners are offered this book of diagnostic principles as an aid to the earlier recognition of surgical lesions. Much space is given to the neurologic examination, including a study of the cranial nerves, the cerebrum, the cerebellum, the spinal cord and the reflexes. A section on spinal fluid ends with elaborate tables showing the findings in health and disease, and in spinal subarachnoid block. The final section considers Roentgen ray diagnosis of the skull and spine, together with methods for obtaining encephalograms, ventriculograms and lipiodol investigations of the spinal cord. Many pertinent photographs aid in the interpretations.

N. Y.

**FRACASTORO. SYPHILIS OR THE FRENCH DISEASE.** A Poem in Latin Hexameters. By GIROLAMO FRACASTORO. With a Translation, Notes and Appendix by HENEAGE WYNNE-FINCH, M.A. (OXON.), and an Introduction by JAMES JOHNSTON ABRAHAM, C.B.E., D.S.O., M.A., M.D. (DUB.), F.R.C.S. Pp. 253; illustrated. London: William Heinemann, Ltd., 1935. Price, 10/6.

WE welcome this latest edition to Fracastorius literature. A well chosen Introduction (38 pages) gives even those readers who have no previous

knowledge of the subject a good background of the views of the origin of syphilis and its remarkable spread through Europe at the end of the 15th century, of the use of mercury and guaiac; of the word "syphilis," with details of Fracastoro's life and the high lights of the subsequent history of syphilis. The Translator's note includes an interesting bit of bibliographic detective work, namely, Fulton's discovery in the Bibliothèque Nationale's copy of a note in Fracastoro's own hand as to the two debatable lines which were added in his handwriting in that copy, but only occasionally included in texts: The prose translation aims to reproduce the author's meaning accurately and yet retain as far as possible the grace and charm of the original—the goal of every translator worth his salt. On the former of these points we are not competent to express an opinion; the latter has been achieved as well as the flowery, circumlocutory style of the 16th century will readily permit. The rather copious notes, footnotes and in the appendices, are unobtrusive helps to further understanding. E. K.

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MARTINI'S PRINCIPLES AND PRACTICE OF PHYSICAL DIAGNOSIS. Edited by ROBERT F. LOEB, M.D., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University, and Presbyterian Hospital, New York. From the authorized translation by GEORGE J. FARBER, M.D. Pp. 213; 30 illustrations. Philadelphia: J. B. Lippincott Company, 1935. Price, \$2.00.

"Our first problem is to indicate the ways and means by which the physician may use his senses for the recognition and evaluation of disease. In this attempt the mention of the more important signs and to some extent also their arrangement will be a valuable and essential means to to this end. . . . Innumerable newly developed diagnostic procedures have been described during the last decades. Yet the simpler method of the practising physician have remained the same. This book is devoted to the physical methods of the latter." (From the Author's Preface.)

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PHYSIOLOGY IN MODERN MEDICINE. By J. J. R. MACLEOD, M.B., LL.D., D.Sc., F.R.C.P., F.R.S., Regius Professor of Physiology in the University of Aberdeen, Scotland, etc. Assisted in the present edition by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, EDWARD P. CARTER, Adjunct Professor of Medicine, Johns Hopkins University and Associate Physician, Johns Hopkins Hospital, N. M. D. OLMSTED, Professor of Physiology, University of California, J. M. PETERSON, Lecturer in Experimental Physiology, University of Aberdeen, and N. B. TAYLOR, Professor of Physiology, University of Toronto. Pp. 1154; 297 illustrations, including 7 plates in colors. Seventh edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$8.50.

It is to be hoped that the recent death of the author of this well-known work will not prevent its continuation in future editions as one of the standard texts on physiology in English-speaking countries. Among the five assistants in the preparation of this edition there is surely sufficient talent to ensure the adequacy of future revisions. The book at last takes its proper status by omitting "Biochemistry" from its title. There have been slight modifications throughout, the chief improvements being the revision by Bard of the chapter on Neuromuscular Mechanisms, and the assembling of the revised bibliography at the end of the volume instead of each section.

E. K.

BLOOD GROUPS AND BLOOD TRANSFUSION. By ALEXANDER S. WIENER, A.B., M.D. Pp. 220; 41 illustrations and 72 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, \$4.00.

To Bernheim's, Feinblatt's and Snyder's books on this subject is now added a work by one who has himself contributed notably to the knowledge of the problem involved. This work, adequately but not exhaustively documented, presents in 18 chapters such topics as the history of, indications for and technique of blood transfusion, the four blood groups with the various nomenclatures and the newer subgroups, and a rather full discussion of the genetic factors involved. It closes with chapters on relation of blood groups to clinical medicine and other medicolegal applications. It will be a useful aid to anyone wishing an authoritative statement of the subject in its latest developments. E. K.

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DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.P.C.P. (EDIN.), Assistant in Dermatology, University of Kansas, School of Medicine. Pp. 1433; 1310 illustrations and 11 colored plates. Ninth edition, revised and enlarged. St. Louis: The C. V. Mosby Company, 1935. Price, \$12.50.

THIS ninth edition in 20 years of a deservedly popular work, revised and enlarged, reflects the continuous expansion of dermatologic studies and publications. Some two score new conditions are here described for the first time. A notable feature, in this as in other recent Mosby books, is the water-proof, vermin-proof cloth binding in which the text is enclosed. E. K.

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THE CARE OF THE AGED, THE DYING AND THE DEAD. By ALFRED WORCESTER, M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 77. Springfield, Ill.: Charles C Thomas, 1935. Price, \$1.00.

THIS little book with the big title was written especially to interest younger medical practitioners in one phase of the art of medical practice. There is a chapter on each of the three divisions of the title. In the care of the aged the physician is urged to devote more attention to the patient's comfort and less time to efforts at impossible rejuvenation. There are many interesting suggestions for the tactful handling of patients. The advice on diet and care of the demented is of special note. There is practically no mention of drugs. Several questionable broad statements are made, such as, "in the prevention of suffering, prostatectomy, for instance, is second only to the discovery of anæsthetics." While the information is more or less general it is none the less interesting. The average physician probably devotes too much thought to the scientific treatment of his patients, young as well as old, and too little attention to their actual comfort.

The chapter on the care of the dying shows the author's unusual and sympathetic understanding of the very last comforts of the patient.

In the care of the dead we see the folly of elaborate and expensive burials and the injustice to future generations by our present sequestrations of land for graveyards.

While this is not a treatise on scientific medicine it is nevertheless an entertaining and instructive book for physicians, and has the advantage of brevity. N. B.

**USEFUL DRUGS.** A List of Drugs Selected to Supply the Demand for a Less Extensive *Materia Medica*, with a Brief Discussion of Their Actions, Uses and Dosage. Edited by ROBERT A. HATCHER, PH.M., Sc.D., M.D., and CARY EGGLESTON, M.D. Prepared under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association: Pp. 203. Ninth edition. Chicago: American Medical Association, 1934. Price, 60 cents.

"THIS book represents a valuable and increasingly effective phase of the efforts of the Council on Pharmacy and Chemistry on behalf of rational therapeutics. Since its first appearance, in 1913, it has become a recognized work in its field. It has been adopted as a textbook by teachers of therapeutics in the best medical schools and by various examining and licensing boards. The various editions and revisions since that time have been undertaken in the effort to keep it abreast with the advance of therapeutics. Drugs that have become obsolete have been deleted, and others the value of which has become established have been added. The statement of actions, uses and dosage of the various drugs are revised after discussion by the whole Council. They represent the latest and best results of therapeutics and pharmacologic revision." (From Review in *J. Am. Med. Assn.*)

**JOURNAL OF TECHNICAL METHODS AND BULLETIN OF THE INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUMS**, No. XIV. Edited by MAUDE E. ABBOTT, M.D., McGill University, Montreal. Editorial Board: WILLIAM BOYD, Winnipeg, Man.; VICTOR C. JACOBSEN and ROBERT A. MOORE, New York City; CARL V. WELLER, Ann Arbor, Mich. Pp. 134; 30 illustrations. Montreal: The Medical Museum, McGill University, 1935. Price, \$2.00.

THIS journal contains too many articles of interest to make selective comment possible or desirable. Turning from the pithy editorials to the original communications, the morphologist is equally "intrigued" by the articles on museum administration and technique, photographic and microscopic technique, and the six short articles on various types of cardiovascular anomalies. Would that circumstances permitted a more extensive presentation at more frequent intervals!

E. K.

**METHODS OF TREATMENT.** By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, Kansas City General Hospital, etc. With chapters on special subjects by H. C. ANDERSSON, M.D., URSULLA BRUNNER, R.N., J. B. COWHERD, M.D., PAUL GEMPEL, M.D., H. P. KUHN, M.D., CARL O. RICHTER, M.G., F. C. NEFF, M.D., E. H. SKINNER, M.D., E. R. DEWEESE, M.D., and O. R. WITHERS, M.D. Pp. 879; 102 illustrations. Fifth edition. St. Louis: The C. V. Mosby Company, 1935. Price, \$10.00.

"THIS book was planned to furnish an outline of all the methods of treatment in internal medicine. Its design contemplates gathering together material otherwise widely scattered in medical literature, as, for instance, descriptions of the technic of spinal puncture, blood transfusion, the wet pack and the ketogenic diet. In the sections on treatment in texts on the practice of medicine a method is recommended usually without any instructions as to technic, usually, indeed, without any discussion of the rationale behind it. Texts on therapeutics and pharmacology are usually devoted

exclusively to drugs. Here all therapeutic procedure is brought together within the compass of one volume. . . . A word concerning the arrangement of the material may be helpful. The first part describes each procedure under the heading of drugs, diet, hydrotherapy, etc. The second considers the application, the results to be expected, etc., under the heading of the various diseases. The advantage of the arrangement is the lack of necessity for repetition. Thus in Part I the action of digitalis dosage, preparations, etc., are set down. In Part II whenever digitalis is indicated or contraindicated, in heart failure, pneumonia, thyrotoxicosis, etc., it is necessary to refer only to the description in Part I in each case." (From Author's Preface.)

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**THE 1934 YEAR BOOK OF PEDIATRICS.** Edited by ISAAC A. ABT, D. SC., M.D., Professor of Pediatrics, Northwestern University Medical School; Attending Physician, Passavant Hospital, etc. With the collaboration of ARTHUR F. ABT, B.S., M.D., Associate in Pediatrics, Northwestern University Medical School; Adjunct Attending Pediatrician, Michael Reese Hospital, etc. Pp. 541; 74 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, \$2.25.

It is difficult to present a fair review of a volume which presents in such compact form a great variety of material. In general, one can say that the editor and his collaborator has covered the year's output of pediatric literature completely. They have made a good selection of material, abstracts of which convey enough information to satisfy the average reader. Some of the abstracts of more thought provoking papers will influence the industrious reader to seek the original articles. In the main, those papers which presented research work of an ultrascientific nature have been slighted and no attempt has been made to choose material from the literature of the fundamental sciences which might have later significance in pediatrics.

However, the volume should be of great value to the busy practitioner who desires accurate, readable abstracts of the recent literature in this field.

E. T., Jr.

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**DOCTORS AND JURIES.** The Essentials of Medical Jurisprudence. By HUMPHREYS SPRINGSTUN of the Detroit Bar. Pp. 155. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, \$2.00.

AMERICAN books on legal medicine are sparse, and British law varies from ours considerably. This small and inexpensive book, designed by a lawyer for doctors, lawyers and others wanting knowledge of the relations of law to medicine should fill a gap. The 18 brief chapters cover such topics as contracts, negligence, damages, burden of proof, testimony, insanity and so on.

E. K.

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**KLINIK DER ERKRANKUNGEN DES HERZMUSKELS.** X. Fortbildungs-Lehrgang in Bad-Nauheim. 20-23 September, 1934. Herausgegeben von der Vereinigung der Bad-Nauheimer Ärzte. Pp. 170; 63 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 70.

SINCE 1920 these volumes have been presenting, almost annually, articles by leaders in their profession on various phases of heart disease. The previous volumes have been on such general topics as Treatment of Cardiac Insufficiency, Modern Methods of Diagnosis, Hypertension, the Arrhythmias, Cardiac Neuroses—all with considerable emphasis on treatment. The present volume treats of myocardial disease from the points of view of anatomy, electrocardiography, radiology, clinical pictures and treatment. Aschoff's articles on myocardial disease not the result of vascular lesions and Hochrein's on cardiac circulation and cardiac pain should prove of especial interest to many.

E. K.

THE 1934 YEAR BOOK OF OBSTETRICS AND GYNECOLOGY. *Obstetrics*. Edited by JOSEPH B. DE LEE, A.M., M.D., Professor of Obstetrics, University of Chicago Medical School, etc. *Gynecology*. Edited by J. P. GREENHILL, B.S., M.D., F.A.C.S., Associate Professor of Gynecology, Loyola University Medical School; Professor of Gynecology, Cook County Graduate School of Medicine. Pp. 717; 96 illustrations. Chicago: The Year Book Publishers, Inc., 1935. Price, \$2.50.

For those who wish to keep abreast of the most important obstetrical and gynecological literature this edition offers a splendidly prepared digest of the subject in American and foreign journals.

The obstetrical division has been prepared by De Lee for the thirtieth time. His frequent comments, terse, pungent, and at times caustically critical, add a piquantly personal sauce to many of the abstracts.

Greenhill has carefully reviewed the gynecological literature. There is no chaff here, and again the comments serve to emphasize the worth of the original articles.

The volume containing references to 652 articles and reproducing 96 illustrations from the original texts forms an indispensable aid to both teacher and practitioner.

P. W.

RATS, LICE AND HISTORY. Being a Study in Biography, Which After Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals with the Life History of Typhus Fever. By HANS ZINSSER. Pp. 301. Boston: Little, Brown & Co., 1935. Price, \$2.75.

It must be said at the beginning that the title of this book would read more properly, "Rats, Lice, History and Dr. Hans Zinsser." It is, in effect, not the "biography" of typhus which it claims (with tongue in cheek) to be, but the apocalypse of an ebullient scientist whose mental and emotional horizon reaches far beyond the walls of his laboratory. Were there an index to the book, which most unfortunately there is not, omitted supposedly as a *beau geste* to the layman for whom the book is primarily intended, it would be found to contain an array of names, pertinent and impertinent (Aristotle—Stein, Gertrude), which would do credit to the omniscient daily book-reviewer of the *New York Times*. The variety of grist required by Dr. Zinsser's mill is, if we may be permitted a contemporary term of understatement, colossal.

The book is, more or less frankly, a thoroughly successful exercise in the current vein of "popular science" writing, not unrelated to similar, and highly popular, works by certain of the author's colleagues, works toward which he, unfortunately under the circumstances, permits himself a derisive gesture. As such, it has much indeed to offer the *homo incognitus* for whom it is intended. Its historical information on typhus is derived not only from the most eminent authorities (to whom credit is scrupulously given, and given, from a literary standpoint, with considerable adroitness), but in many cases from the author's own recourse to original sources. The information, moreover, is frequently of poignant interest. And it is not likely that on the author's own ground—the technical elucidation of the typhus virus, its etiology, and habits—anyone will be tempted to question Dr. Zinsser's right to speak with the voice of authority.

The book is philosophically discursive in the grand manner of Sterne and Melville and others of the elect. Its greatest appeal will be to those fortunate enough to capture from its somewhat determined roguishness the same mental stimulation and zest which undoubtedly went into the writing of it. They will unquestionably be many and not at all disturbed, rightly, by the remaining few who still deem it a hopeful symptom of maturity, generally speaking, to count ten.

W. McD., 2d.



## NEW BOOKS.

*Journal of Technical Methods and Bulletin of the International Association of Medical Museums*, No. XIV. Edited by MAUDE E. ABBOTT, M.D., McGill University, Montreal. Editorial Board: WILLIAM BOYD, Winnipeg, Man.; VICTOR C. JACOBSEN and ROBERT A. MOORE, New York City; CARL V. WELLER, Ann Arbor. Pp. 134; 30 illustrations. Montreal: The Medical Museum, McGill University, 1935. Price, \$2.00. (Review, p. 867.)

*Le Nodule de la Corde Vocale*. By JEAN TARNEAUD, Oto-Rhino-Laryngologiste de l'Hôpital Bellan et du Conservatoire national de Musique de Paris. Pp. 139; 24 illustrations. Paris: Norbert Maloine, 1935. Price, 30 fr.

*Names of Surgical Operations*. Compiled and Arranged by the Western Surgical Association Through Its Special Committee. Edited by CARL E. BLACK, A.M., M.D., Jacksonville, Ill. Pp. 102. St. Paul, Minn.: Bruce Publishing Company, 1935. Price, \$3.00.

"The work of the Committee of the Western Surgical Association in the preparation of a standard nomenclature for surgical operations represents an enormous amount of painstaking labor and will prove of the greatest assistance to all hospital record librarians, as well as to the surgeons who are obliged to use hospital records for the collective study of clinical material. It is perhaps to be regretted that the identification of certain standard operations by the names of their originators must be abandoned in favor of the anatomic term describing the procedure employed, but the sentimental objection must give way to the practical point of accuracy." (From Dr. Greenough's Foreword.)

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*Koronarinfarkt und Koronarinsuffizienz*. In Vergleichender Elektrokardiographischer und Morphologischer Untersuchung. By PROF. DR. MED. FRANZ BÜCHNER, Vorstand des Pathologischen Instituts am Horst-Wessel-Krankenhaus der Stadt Berlin, PROF. DR. MED. ARTHUR WEBER, Vorstand des Balneologischen Universitätsinstituts in Bad-Nauheim, and DR. MED. BERTHOLD HAAGER, Assistent am Balneologischen Universitätsinstitut in Bad-Nauheim. Pp. 104; 116 illustrations. Leipzig: Georg Thieme, 1935. Price, Rm. 15.

*A Suggestion for an Experimental Trial of Alum-treated Formalized Virus in the Active Local and General Immunization Against Poliomyelitis*. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 11. Cleveland: Mount Printing Company, 1935. (Price not given.)

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*A Textbook of Biochemistry*. Edited by BENJAMIN HARROW, Ph.D., Associate Professor of Chemistry, The City College, College of the City of New York, and CARL P. SHERWIN, M.D., Sc.D., Dr.P.H., LL.D., Member of the Staff of St. Vincent's and French Hospitals, New York. Pp. 797; 52 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, \$6.00.

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- Atlas Fundus Oculi.* By WILLIAM HOLLAND WILMER, M.D., LL.D., Sc.D., Professor of Ophthalmology and Director of the Department of Ophthalmology of the Johns Hopkins University School of Medicine, Ophthalmologist-in-Chief to the Johns Hopkins Hospital, etc. Introduction by WARFIELD T. LONGCOPE, M.D., Professor of Medicine and Director of the Department of Medicine of the Johns Hopkins School of Medicine. Pp. 100; 100 colored plates. New York: The Macmillan Company, 1934. Price, \$35.00. (Review, p. 862.)
- The Harvey Lectures, Series 29.* Delivered under the auspices of The Harvey Society of New York, 1933-1934. Under the patronage of the New York Academy of Medicine. By Drs. R. E. DYER, W. M. CLARK, R. G. HARRISON, E. A. DOISY, E. A. GRAHAM, G. L. STREETER, T. M. RIVERS and D. W. BRONK. Pp. 262; illustrated. Baltimore: The Williams & Wilkins Company, 1935. Price, \$4.00.
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- The Kidney in Health and Disease.* Edited by HILDING BERGLUND, M.D., Stockholm, Sweden, formerly Chief of the Department of Medicine at the University of Minnesota, and GRACE MEDES, Ph.D., Research Biochemist in the Lankenau Hospital Research Institute, Philadelphia. With the collaboration of G. CARL HUBER, M.D., Professor of Anatomy and Director of Anatomical Laboratories and Dean of the Graduate School of the University of Michigan, WARFIELD T. LONGCOPE, M.D., Professor of Medicine in the Johns Hopkins University, Baltimore, and ALFRED N. RICHARDS, Ph.D., M.D., Professor of Pharmacology in the University of Pennsylvania, Philadelphia. Pp. 754; 163 illustrations. Philadelphia: Lea & Febiger, 1935. Price, \$10.00.

## NEW EDITIONS.

- Diseases of the Heart.* By JOHN COWAN, B.A., M.D., D.Sc., F.R.F.P.S., sometime Professor of Medicine, Anderson College of Medicine, and Consulting Physician, Royal Infirmary, Glasgow, and W. T. RITCHIE, O.B.E., M.D., F.R.C.P.E., F.R.S.E., Professor of Medicine and of Clinical Medicine, Edinburgh University, and Physician to the Royal Infirmary and Director of the Medical Unit of the Municipal Hospitals, Edinburgh. With a chapter on The Ocular Manifestations of Arterial Disease by ARTHUR J. BALLANTYNE, M.D., F.R.F.P.S., Lecturer on Ophthalmology, University of Glasgow, and Surgeon, Eye Infirmary, etc. Pp. 631; 335 illustrations, some in colors. Third edition. Baltimore: William Wood & Co., 1935. Price, \$9.00.

Almost entirely rewritten to keep up with the many recent advances, this book presents tersely the individual views of two foremost authorities in a country that has been a leading contributor to the subject. The authors do not accept the newer terminology for extrasystoles and bundle-branch block.

- Recent Advances in Endocrinology.* By A. T. CAMERON, M.A., D.Sc. (Edin.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba, and Biochemist, Winnipeg General Hospital. Pp. 406; 55 illustrations, including 2 plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, \$5.00.

# PROGRESS OF MEDICAL SCIENCE

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## NEUROLOGY AND PSYCHIATRY

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UNDER THE CHARGE OF

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### DEPRESSIVE REACTIONS IN GENERAL PRACTICE.

NEXT to the psychoneuroses there is probably no other mental disorder met so frequently in the general practice of medicine as the depressive reactions, described by Meyer<sup>1</sup> as "biologically widespread reactions of great individual and social importance, recognizable largely as preoccupations and fixations of the pure affects of sadness and anxiety dependent upon various experiences as bereavement and losses with active or passive suffering." Comprised in this group is that large number of individuals who come to the physician with somatic complaints of one kind or another—head sensations, stomach upsets, pains, aches, constipation, tired feeling, poor sleep and appetite. The physical examination shows appreciably little to account for the sweeping nature of the complaint while diet, teeth extractions, rest cures, and fishing trips fail to solve the problem.

At this point the conscientiously curious physician will investigate further and will learn that the illness had a definite beginning, was precipitated by clear cut situational factors usually in line with personal disappointments or losses to which the patient had responded with worry, anxiety, and concern. The physician will be informed that blueness and sadness best characterize the patient's feelings; that, because of inappetence, he has lost weight, that he is constipated, and that his sex drive is less keen. He may add that generally his spirits improve as the day wears on, though in the morning "life seems unbearable" and that his concentration and memory are "shot." The frequency with which such a patient finds his way to the general practitioner is demonstrated by the report of liaison psychiatry at the Colorado General Hospital<sup>2</sup> where, of 245 cases seen in the 7 months' period, 16.3% were depressions or showed depressive features of primary importance.

Definitely differentiating depressive reactions from the psychoneuroses, or part reactions, is their sweeping character, their biological components—sleep disturbance, loss of weight, constipation, poor

appetite, decreased libido—that point to more serious and widespread involvement of the personality. It is these factors of a biologic nature, associated with suicidal preoccupation so commonly a part of the depressive reactions which call for the most careful consideration by the physician who encounters them.

Though opposed to the tendency of nosological pigeon-holeing, we favor Harrowes'<sup>3</sup> classification of the depressive reactions for the merit it holds in the direction of evaluating etiology and prognosis. He points out six depressive patterns, namely: (a) reactive, (b) autogenous, (c) recurrent, (d) psychoneurotic, (e) depression with aversion features, and (f) involutional types.

In the reactive group, cases are precipitated by difficulties in the life situation. Symptoms beside the formal depression are lack of concentration, loss of interest, insomnia, loss of thought capacity, heightened sense of effort, forgetfulness and headaches. Self-accusation and suicidal preoccupations are not prominent. Etiologic factors are catastrophic or accumulative. With the latter, the illness is more protracted. Of the personality features, there is unimaginativeness and rigidity. Retardation is not marked and insight is variable.

In the group of autogenous depressions, there is no reactivity beyond the initial precipitation. Feelings of remorse and guilt are more marked there is more distortion, retardation, and rut formation, and the affect is not influenced by general factors in the environment or in therapeutic attempts. Suicidal preoccupations are frequent.

The recurrent depressions reveal a history of previous attacks of severity increasing with age. Here, the personality make-up is more definitely depressive in character and agitation and hypochondriasis tends to be more prominent. They are differentiated from recurrent reactive depressions by their more insidious onset and agitation.

Psychoneurotic depressions are chiefly characterized by a prodromal picture of a psychoneurosis, run along course, and are found difficult to modify.

The depressions with aversion, as the term signifies, demonstrate peevishness, occasional paranoid trends in which the patients blame the environment as a handicapping agent, are antagonistic to any therapeutic approach, possess a definite restriction of utilizable interests and inadequate emotional response.

Harrowes' final group, the involutional types, tend to much greater rut formation, entertain schizophrenic-like hypochondriacal delusions, express nihilistic ideas, occur often in presenile women, and are not infrequently terminated by impulsive suicidal acts.

Psychiatric writers have long pointed out the frequency of hereditary taint in the background of individuals suffering from manic-depressive disorders. It has been left, however, to a certain group of writers to investigate this point from a point of view of genetic laws and order. Pollock, Malzberg and Fuller,<sup>4</sup> in an article concerned with the hereditary features involved in manic-depressive psychoses, pointed out their belief that the frequency of mental disease among siblings of the patients with manic-depressive psychoses is consistent with a mode of inheritance based upon the supposed existence of Mendelian unit characters. These works showed conclusively, by careful case studies, that the frequency of mental disorders among the siblings, especially

of manic-depressive psychoses, is significantly in excess of the total expected, in populations selected at random. This was especially true in connection with the siblings of female probands with manic-depressive psychoses. They conclude that there is a familial basis for the development of mental disorders in many cases though the underlying laws of their manner of transmission are not yet understood.

Calling to the attention of the practitioner a particular type of depression frequently masked by the predominance of somatic complaints, is Muncie's article, "Depression with Tension."<sup>5</sup> This group of patients are seen with complaints frequently expressed as the following: "My nerves feel like rubber bands—all a-quiver," "The skin feels stretched over my forehead," "It seems as though there are bubbles and needles in my muscles," "I have the sensations of worms crawling over my skin." Or again, the complaints may be of shooting pains, numbness, trembling, burning, weakness, and quivering in the stomach. In addition to these more obvious physical complaints there are those common to all depressed patients—insomnia, anorexia, and loss of weight. Despite the rather subordinate statements of mood given by these patients, they are invariably observed as sad, brooding, or disinterested, and it is a subordination of mood to the somatic complaints which frequently leads to a wrong diagnosis. Careful investigation procedure revealed the fact that this illness is strongly reactive. In the author's survey of cases, he found that about one-half the group were reactive to sexual difficulties, the others reactive to work dissatisfaction—perhaps promotion, demotion, or the feelings that the responsibilities enforced upon the individual exceeded his capacity to handle them. In this group of depressions, the author found that the situations which lay at the bottom of the problem were still open issues and held possible disaster for the future. In this respect the tension depression differs from the retarded depression in that, in the latter, the patient shows his concern over past events and closed issues. The physiologic expression of tension in these cases is demonstrated by tachycardia, labile pulse, abnormal curve of dextrose tolerance, abnormal findings of gastric secretion, either hypo- or hyper-chlorhydria, exophthalmos, tremors, sweating, flushing, diarrhea, seminal emissions, or an increased sex desire. The evidences of depression are expressed in the mood which is characterized by the patient as "melancholy," "blue," "bleeding if I were to die," "I have given up fighting," "I feel a moral weakling," and, objectively, in the appearance of the individual an obvious morning evening variation of mood. The physiologic evidences are again present but perhaps less classical than in other types of depressions. The appetite is usually good, the weight may vary, and there is constipation in about two-thirds of the cases. The sleep demonstrates all manner of variation, though early morning waking is found more frequently than any other type, and irregularities of the sex rhythm may be manifest.

The usual personality background of the tension depression is that of one who is superficially well adjusted, who is accustomed to getting his own way, who is rigid, tenacious, aggressive, and dependent upon his environment. These people usually take responsibilities very seriously, and, as a rule, are very successful in their undertakings. Hypochondriacal trends usually are not a part of the prepsychotic make-up.

Emancipation problems loom prominently in these individuals. The treatment outlined by the author consists essentially of prolonged hospitalization and the obligation of the family to assume all responsibility for the suicidal risk should the patient leave the hospital prematurely. He found that loose, cold, wet packs decreased tension and induced sleep and that, further, the tension could be minimized by small broken doses of barbitol,  $2\frac{1}{2}$  grains, q.i.d. Belladonna and alkalis were administered in vagotonic gastric intestinal symptoms. He pointed out that the most reliable indications of progress were to be found in paying close attention to the sleep chart, weight graph, and behavior manifestations. Needless to say, a careful, thorough, critical appraisal of the personality was undertaken when the patient was capable of carrying on such an analysis.

Michael<sup>6</sup> defines affect as an awareness of the changes in the body from the impact of environment, or the product of changes in biologic equilibrium from within. The therapeutic approach in affective disorders must follow along lines of causation, somatogenesis, and psychogenesis. Psychotherapy is not limited to psychologic technique but includes all those methods that may be employed in the management of an individual case. Attempts should be made, first, to determine the patient's inherent endowments and constitutional make-up. The therapist must have a reasonable impression of the family setting, the emotional and intellectual development and the social and economic situations. Investigation of the bodily systems is an important consideration. After the therapist has insight into the situations that may be present, or of the disturbing experiences of earlier life that lie at the basis of the patient's reaction, he will decide on the particular method of psychotherapy. He first gives attention to the organic factors and then considers the following: persuasion, suggestion, psychologic reëducation, or personality analysis. The last three methods are most desirable.

The social consideration of this important clinical problem is well brought out in a study of 100 cases of suicide made by Fairbank<sup>7</sup> at Hopkins. Of the 100 cases selected for the survey, 47 were women and 53 men. Seventy-three of them presented "outspoken depression," and 17 of the 24 paranoid and schizophrenic cases showed at least "depressive waves." In the experience of the writer, the motivating factor seemed to be a desire to escape from the mental suffering, from fears or trying environmental situations and disappointments. In more than one-half the cases, the words "hopelessness" and "despair" were encountered. Also, a frequent occurrence was the conviction by the patient that he was "losing his mind" or "going crazy." Spite appeared to be the motive in a few cases while escape from delusional persecution was also found. Two of the group committed suicide to avoid actual situations they could not face.

The writer pointed out as warning signals of suicide the following utterances of patients: "I am an empty shell," "I am guilty," "I am going crazy," "There is no hope for me," and "It is no use going on." The personality characteristics commonly encountered in this group were rigidity, stubbornness, and lack of plasticity. As other writers have shown in the history, depression or other instability was frequently found in collaterals. The methods utilized in suicidal attempts, inter-

estingly enough, were often determined by the prevailing social custom or "style" as indicated in the frequent newspaper reports. The only clinical correlation to be drawn was that perhaps suicide in the schizophrenic was of a more bizarre nature. That there is, as a rule in most cases, warning, this author feels quite sure. Her survey revealed the facts that one-third of the cases gave a very definite indication of danger by having made a previous attempt at suicide and an additional one-third suggested their intention by taking about it. There were 14 cases which gave no intent in this direction or indication other than their tension and restlessness associated with the depression. -

In the handling of the potentially suicidal individual a great many problems arise. Premature discharge from the hospital, placing on suicidal observation, guarding against environmental devices which invite the act—all are considerations of importance. Dr. Fairbank points out these warnings and problems and urges prevention by regulations governing the sale of destructive agents because "physicians, the nurses, and the friends of the 'suicide' have reason to feel that with better knowledge and greater care and attention, it might have been possible to prevent what is usually a serious trauma to the unsuccessful and a deplorable event to everybody."

FRANKLIN G. EBAUGH, M.D.

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#### OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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#### RELATIONS WITH ADJACENT STRUCTURES.

THERE is a far greater tendency to think of infection spreading to the meninges and brain through some loss of continuity of the bone, such as a congenital dehiscence, a fracture, or some operative trauma than by the blood stream. Therefore, such contiguous pneumatic spaces as the frontal and sphenoid sinuses, the middle ear and mastoid are often accused when in reality the original focus is somewhere more

remote. On our neurosurgical service we have recently had a brain abscess following a peritonsillar abscess and another following a maxillary sinus infection without an osteomyelitis. It is, therefore, very timely that Julius Berendes<sup>1</sup> reports a frontal lobe abscess following an abscess of the septum. This was proven by autopsy. He rightfully states that much has been written about front lobe abscess as a complication of sinus disease, but that in the German literature of the past 12 years no such case as this has been reported. There has been much written about meningitis as a frequent complication of a septal abscess, but none of brain abscess. His case was in a boy, aged 14 years. The abscess was drained. However, on the 19th day the boy developed meningeal signs and unconsciousness. The frontal sinuses were opened and found to be clear. Further operation was refused. Postmortem examination revealed a left frontal lobe abscess, and it was believed that the infection entered the brain by the anterior and posterior ethmoid vessels.

The practice of medicine includes dentistry, and dentistry is a special branch of medicine. To secure efficient coöperation between the two, the dentist should first have a reasonable medical background, and secondly the physician should know sufficient dentistry to understand dental points of view and values. The dentist must recognize the fact that any departure from the normal in the mouth may be the cause, the effect or the symptom of organic disease in other parts of the body. For example, pallor of the skin or mucous membrane should suggest an anemia; edema of the eyelids, a nephritis; enlargement of the thyroid or exophthalmos suggest thyroid investigation; diseased tonsils and adenoids may require attention; an acetone breath should suggest diabetes. Oral syphilis, neoplasms and leukoplakia are frequently seen. The physician should detect the presence of caries, periodontoclasia, malocclusion, poor dental hygiene, fistulas and Vincent's infection. The coöperation of the dentist and the obstetrician in the care of the teeth in the expectant mother is most important. The pediatrician should also know of the harmful habits of thumb sucking, tongue biting, lip interposition and mouth breathing, and of their effect on distorting perfect arches.

The prevention of disease is the cheapest and yet the best service that we can give the public, and for that reason should occupy the most important place in dental and medical education and practice. Next to prevention, the early recognition of disease is the greatest necessity and of the highest service to the public.<sup>2</sup>

A cholesteatoma has been defined by Kopetsky<sup>3</sup> as a globular growth surrounded by a thin shell of epidermis and connective tissue, called the matrix, and composed of accumulated, stratified, horny, desquamated epithelium, devoid of nuclei. Between its lamellæ are found cholesterol crystals in a greater or lesser quantity.

Wittmack<sup>4</sup> explains the formation of cholesteatoma as an attempt by Nature at repair by the growth of the squamous epithelium of the external auditory canal into the middle ear to replace the degenerating mucous membrane. In 1879, Mikulicz,<sup>5</sup> a pathologist, was the first to suggest that cholesteatomatous tumors could arise from an embryonal rest of epidermis. The occurrence of a cholesteatoma in the temporal bone became comprehensible under this theory, since the pinching off



of an epidermal "anlage" in the embryonal sutures is a possible occurrence during the development of the middle ear.

Today we recognize both primary and secondary types of cholesteatomata of the temporal bone, arising from a transplantation of foreign tissues and their growth, the primary being congenital, and the secondary being "postfetal." Anatomically they present the same picture. A secondary cholesteatoma may be identified when there has been a history of earlier or present middle-ear disease.

Day<sup>5</sup> has stated that whether the cholesteatoma is primary, arising from an invagination, pouching and rupturing of Schrapnell's membrane following the formation of adhesions, walling off the attic, or from the middle ear in an infantile otitis of the catarrhal type, or is secondary to a suppurative otitis with an ingrowth of the epidermis of the external canal through a marginal perforation into the middle ear and attic, its development is the same, though the suppuration is a result of the former and the cause of the latter.

The cases diagnosed as primary cholesteatoma of the temporal bone after critical observation are rare and seem to show a predilection to develop in the region of the junction of the temporal, parietal and occipital bones. Recently Beck<sup>6</sup> has reported such a case and has added some interesting remarks about the "art und weise" of the operation performed.

The patient was a girl, aged 20 years, who had had some right-sided deafness for 6 months. Then the development of a facial paralysis sent her to a doctor. At this time the right ear drum looked normal, but there was some deafness. Upon her first examination the vestibular responses were present, but 4 years later upon examination they had disappeared. At this time the patient tended to lean to the right on walking. Roentgen ray showed a large pneumatic mastoid. A Roentgen ray of the petrous tips by Stenver's technique showed a tumor mass, 2 cm. by 1 cm., just under the upper border of the pyramid.

At operation the dura of the middle fossa was widely exposed through the tegmen approach, and by carefully lifting up the dura a cholesteatomatous mass removed, along with as much "matrix" as possible. The patient had a slightly stormy convalescence at first, a positive Kernig and Babinski and a cloudy spinal fluid. In 3 weeks she was out of bed and was discharged at the end of 5 weeks. Electrical treatments were given to the face and the facial weakness was not noticeable after 3 months' time. The deafness and caloric reactions remained unchanged. The author stated that should there be a recurrence from leaving behind some of the matrix he would sacrifice the labyrinth to avoid a recurrence of the facial paralysis. Calcination of the matrix has been observed and Linck has written of findings giving expression to former reports of cell degeneration in the epithelium of the matrix.

In an analysis of 230 patients with carcinoma of the tonsil by Schall,<sup>7</sup> its frequency was found to be 1 in every 106 cancer patients. There appears to be no evidence of increase since 1918. The patient's nationality and occupation did not seem to be factors. The male sex contributed 88.7% of the cases. The age group is that of past middle life. The greatest incidence is found in the group between 60 and 65 years. Only 18 patients gave a family history of carcinoma. There were 42 patients who were non-users of tobacco. In only 48 cases was the

disease limited to the tonsil. In 104 patients the first symptom was pain. The majority of these patients endured their symptoms from 3 to 6 months before consulting a physician. Glandular enlargement occurs fairly early. Cancer of the tonsil was first treated surgically, later by electrosurgery, diathermy or electrocoagulation, and now by the combined use of radium and high-voltage Roentgen ray therapy. In 118 cases in which this treatment was given, 43 cases had no relief, 47 recurred under 1 year; 2 in 1 to 2 years; 2 in 2 to 5 years; and 1 case recurred after 5 years. Of the 23 cases who had no recurrence (18.4%), 5 had died a non-cancerous death.

A new surgical approach to the base of the tongue and lower pole of the tonsil for neoplasm has recently been devised by Dr. D. Macpherson and his associate, Dr. A. Newlands. The operation is done in two stages, the first stage being a tying off of the external carotid artery. A cutting diathermy current is used and completely controls bleeding. Several modifications of this operation are also described.

The Shintz and Coutard schools in Europe do not entirely accept the Broder classification of malignancies. They are endeavoring to identify neoplasms in more detail as to their radiosensitivity and radio-resistance. Berven, of Stockholm, reports good results with the use of a 3-gram radium pack. However, the results published by Schall compare favorably with those of Berven and Coutard. Clinically, the results of treatment are encouraging even though a "cure" may not always be obtained.

W. V. MULLIN AND  
W. L. DEETON.

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## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 15, 1935

**The Plexus Omentalis and Its Relation to Capillary Innervation in the Omentum of Rabbits, With Special Reference to the Unmyogenic Character of Rouget Cells.** NICHOLAS A. MICHELS (Daniel Baugh Institute of Anatomy, Jefferson Medical College). By projecting the capillary bed from whole mount preparations of the omentum of

rabbits, then drawing capillary nerves in 325 contiguous oil-immersion fields, a new anatomic support has been found for the physiologic concept of capillary innervation. A nerve plexus was revealed (plexus omentalis) the meshes of which are considerably wider than those of the capillary plexus itself. It consists of numerous non-medullated nerve fibers which pertain to the category of plasmodial nerve strands (Remak fibers), now regarded as the ultimate terminations of the autonomic system. The 1-micron wide Schwannian nucleated capillary nerves run parallel, cross over, under, accompany, and often become lost in the capillary wall. Since many capillaries have no nerves, and since terminal knob-like endings on endothelium were never found (no one has ever seen them with certainty on capillaries), it is concluded that capillary innervation is effected as a physiologic unit, the nervous syncytium functioning at contact points with self-contracting endothelium. In fixed and vitally stained preparations there was no evidence of the muscular character or innervation of Rouget cells. Pericapillary oblong cells prevailingly represent pericytes; a goodly quota have been mistaken for nucleated segments of capillary Remak fibers. A study of living capillaries in the web of the frog under normal and experimental conditions confirmed the contractile power of endothelium and the non-myogenic character of Rouget cells.

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**Effect of Dorsal Root Stimulation on the Properties of the Muscles of Bloodvessels.** EMIL BOZLER (Johnson Foundation, University of Pennsylvania). A study was made of the changes in the properties of smooth muscle under the influence of stimulation of inhibitory nerves. A frog hindleg was perfused. The contractions of the muscles of the arterial system were measured by recording the flow, using a sensitive flowmeter. It was found that dorsal root stimulation suppresses the effect of sympathetic stimulation completely if the stimuli follow one another at long intervals. If they are applied at a high frequency the response is not appreciably influenced by simultaneous dorsal root stimulation. The results can be quantitatively interpreted on the basis of the chemical intermediators. The inhibition seems to be due to an immediate antagonism of the two intermediators produced by stimulation of the sympathetic and the vasodilators without any effect on the contractile mechanism as such. It is, furthermore, found that dorsal root stimulation greatly accelerates the relaxation. From stretching experiments it is concluded that the rate of relaxation is essentially determined by the viscous properties. The experiments give evidence that dorsal root stimulation decreases the viscosity of the muscles of the arteries.

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**The Absorption of Glucose and Galactose From the Dog's Intestine.** F. A. CAJORI and WALTER G. KARR (Laboratory of Physiological Chemistry, University of Pennsylvania). The rates of absorption of glucose and galactose from Thirty loops of the jejunum of dogs have been studied. When solutions containing both these sugars were inserted into the loop, glucose was absorbed more rapidly than galactose, the total carbohydrate absorption being about the same as when the sugars were given separately. However, no difference was found

in the rate of absorption of glucose and galactose when administered separately.

There was no indication that in the presence of phosphates the rate of glucose, galactose or fructose absorption was increased. These results, which are contrary to those reported by Magee and Reid,<sup>1</sup> are of interest when considering the hypothesis that the mechanism of sugar absorption involves phosphorus compounds. The rate of sugar absorption was not changed in the presence of sulphate or chlorid.

One-half to one hour following the administration of isotonic solutions, the osmolar concentration of the loop contents remained close to the accepted value for dog's blood. Water was not absorbed as rapidly as sugar, the absorbed sugar being replaced by chlorid. When the solutions introduced into the intestinal loop had an osmotic pressure twice that of the blood, an hour's time was hardly sufficient for the attainment of osmotic equilibrium. Analysis showed, however, that chlorid had entered the hypertonic solution.

Glycogen was isolated from dog's liver after a period of galactose feeding and compared with dog's liver glycogen isolated after glucose feeding. The two glycogens were hydrolyzed at the same rate with  $H_2SO_4$ , salivary amylase and taka-diastrase. They exhibited the same specific rotation before and after hydrolysis. It was concluded that they were identical chemically.

1. A Study of the Gall-bladder Bile in Pregnancy at Term. 2. A Study of the Gall-bladder Bile in Calculous and Non-calculous Cholecystitis. 3. A Study of White Bile. C. RIEGEL, I. S. RAYDIN, C. G. JOHNSTON and P. J. MORRISON (Laboratory of Research Surgery, University of Pennsylvania). Data on the composition of bile from the human gall bladder in the following conditions were given: (1) In pregnancy at term; (2) in non-calculous and calculous cholecystitis; and (3) in hydrops.

The mean calcium concentrations in all five groups were below normal, the average values being for the pregnancy group (A) 15 m Eq./L.;<sup>2</sup> for the non-calculous cholecystitis group (B), 16 m Eq./L.; for the calculous cholecystitis group in which the gall bladder was visualized after sodium tetraiodophenolphthalein (C), 15 m Eq./L.; for the calculous group in which the gall bladder was not visualized after dye administration (D), 10 m Eq./L.; and in the hydrops group (E), 10 m Eq./L.

The mean chlorid concentrations were above normal in all five groups and the concentration increased with increasing disturbances of biliary tract function. The average values were for (A) 46, for (B) 57, for (C) 61, for (D) 102 and for (E) 113 m Eq./L.

The mean bile salt concentrations were lower than normal in all five groups. The highest values were found in the pregnancy and non-calculous groups, while in hydrops bile salts were absent. Mean values were for (A) 2653, for (B) 2813, for (C) 1560, for (D) 607 and for (E) 0 mg. per 100 cc.

The mean cholesterol concentrations were higher than normal in the first three groups: (A) 376 mg., (B) 383 and (C) 487 mg. per 100 cc.; in (D) cholesterol dropped to 133 and in (E) to 14 mg. per 100 cc.

<sup>1</sup> Magee, H. E., and Reid, E.: J. Physiol., 73, 163, 1932.

<sup>2</sup> m Eq./L. = milliequivalents per liter.

These five groups illustrate progressive stages in the development of a damaged gall bladder and the production of gall stones, the pregnancy and non-calculous groups being the most nearly normal, while the "white bile" group shows the greatest variation from the normal. The condition of lowered calcium and increased chlorid concentration is indicative of damage to the gall-bladder wall. The high cholesterol values in groups (A) and (B) probably indicate that a bile abnormally high in cholesterol is being excreted into the gall bladder from the liver, since there were no indications at operation of an inflammatory lesion of the gall-bladder. The low bile salt concentration may be due to a reduced amount of bile salt in the hepatic bile or to a more rapid absorption of bile salt in the gall bladder. It would appear from the summary of data given here that an increase in cholesterol concentration or a decrease in bile salt, or both, may be the initial factor in stone formation. That these factors alone are not sufficient, however, is evident from the absence of stones in the cases of the non-calculous and pregnancy groups, although in many instances in these two groups there was evidence of both an abnormal hepatic bile and a damaged gall-bladder wall.

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